ACTA RADIOLOGICA

FOUNDED IN 1921 BY GÖSTA FORSSELL

OFFICIAL ORGAN OF THE RADIOLOGICAL SOCIETIES OF DENMARK FINLAND NORWAY AND SWEDEN

THERAPY PHYSICS BIOLOGY

INDICES to Vol 10 (1971)

February April June August October December

Contents of Volume 10 — THERAPY PHYSICS BIOLOGY

Subject index to Volume 10 — Therapy Physics Biology

Radiation Therapy

Hormone therapy

Radioactive isotopes

Radiophysics

Technique

Subject index to Volume 10 — Therapy Physics Biology

Radiation Therapy

Hormone therapy

List of Authors

(r) indicates reviewed only

Radiobiology

Radiation protection

Miscellaneous

Book reviews

189 OLOV DAHL and KARL JOHAN VIKTERLOF Attainment and value of precision in deep radiotherapy Some fundamentals with special reference to moving beam therapy with 200 to 250 kV roentgen rays and cobalt 60 gamma radiation 1960 *Price Sw Kr 35*
190 RUNE SOREMARK Distribution and kinetics of bromide ions in the mammalian body Some experimental investigations using Br^{80m} and Br^{82} 1960 *Price Sw Kr 30*
191 ULF BORELL and INGMAR FERNSTRÖM Radiologic pelvimetry 1960 *Price Sw Kr 30*
192 NILS LINDVALL Renal papillary necrosis A roentgenographic study of 155 cases 1960 (Out of print)
193 PAUL EDHOLM The tomogram Its formation and content 1960 *Price Sw Kr 30*
194 RAIMO KIVILUOTO Pleural calcification as a roentgenologic sign of non-occupational endemic anthophyllite asbestosis (Mineralogic appendix by OLAVI KUOVO) 1960 *Price Sw Kr 25*
195 SVEN SCHELLER Roentgenographic studies on epiphysial growth and ossification in the knee 1960 *Price Sw Kr 35*
196 K A HULTBORN and BO TORNBERG Mammary carcinoma The biologic character of mammary carcinoma studied in 517 cases by a new form of malignancy grading 1960 *Price Sw Kr 35*
197 LARS R HOLSTI The mitotic and radioprotective effect of cysteine and lysine in rat 1960 *Price Sw Kr 30*
198 OSBORNE BARTLEY The isometric relaxation phase of the left ventricle An electrokymographic study 1960 *Price Sw Kr 35*
199 GUNNAR WILLER VESTBY Vaso-seminal vesiculography in hypertrophy and carcinoma of the prostate with special reference to the ejaculatory ducts 1960 *Price Sw Kr 35*
200 BJORN NORDENSTROM Contrast examination of the cardiovascular system during increased intrabronchial pressure 1960 *Price Sw Kr 30*
201 GIOVANNI DI CHIRO RISA encephalography and conventional neuroradiologic methods A comparative study 1961 *Price Sw Kr 35*
202 LARS BJORK Velopharyngeal function in connected speech Studies using tomography and cineradiography synchronized with speech spectrography 1961 *Price Sw Kr 25*
203 BENGT O NYLÉN Cleft palate and speech A surgical study including observations on velopharyngeal closure during connected speech using synchronized cineradiography and sound spectrography 1961 *Price Sw Kr 25*
204 S R KJELLBERG B NORDENSTROM U RUDHE V O BJORK and G MALMSTROM Cardioangiographic studies of the mitral and aortic valves 1961 *Price Sw Kr 30*
205 GUNNAR CARLBERGER Kinetics and distribution of radioactive cobalt administered to the mammalian body 1961 *Price Sw Kr 30*
206 HANS MOELL Kidney size and its deviation from normal in acute renal failure A roentgendiagnostic study 1961 *Price Sw Kr 25*
207 LEIF KULD HANSEN Micturition cystourethrography with automatic serial exposures An opinion on the value of the method 1961 *Price Sw Kr 30*
208 FINN LUNDWALL Cancer of the vulva A clinical review 1961 *Price Sw Kr 30*
209 ILMARI LINDGREN Anatomical and roentgenologic studies of tuberculous infections in BBC-vaccinated and non vaccinated subjects with biophysical investigations of calcified foci 1961 *Price Sw Kr 25*
210 PER ERIK E BERGNER The significance of certain tracer kinetical methods especially with respect to the tracer dynamic definition of metabolic turnover 1962 *Price Sw Kr 30*
211 I VUORINEN P ANTTILA U WEGELIUS A KALPPILA and E KOIVISTO Renal cortical index and other roentgenographic renal measurements 1962 *Price Sw Kr 25*

List of Supplements to Acta Radiologica

Nos 173—312

(Issued December 1971)
For Suppl Nos 1—172 inclusive, see list issued December 1960 in Vol 54 fasc 6

The supplements are published from time to time and are not included in the subscription rate Prices and year of publication of numbers already issued are detailed below

173 Erik Odeblad, Bjorn Westin and Sven Erik Englund Disappearance measurements Theoretical, technical biological and medical aspects 1959 *Price Sw Kr 30*
174 Lars Billing and Erik Severin Slipping epiphysis of the hip A roentgenological and clinical study based on a new roentgen technique 1959 *Price Sw Kr 35*
175 Åke Hanngren Studies on the distribution and fate of C^{14} and T labelled p amino salicylic acid (PAS) in the body 1959 *Price Sw Kr 25*
176 Lars Bjork Cineradiographic studies on the Fallopian tubes in rabbits 1959 *Price Sw Kr 25*
177 Pekka Vuorinen The roentgenographic slit methods A survey and analysis of procedures based on the use of a narrow bundle of roentgen rays (scanography) 1959 *Price Sw Kr 25*
178 Bengt H O Rosengren Determination of cell mass by direct X ray absorption 1959 *Price Sw Kr 25*
179 S Hultberg, O Dahl R Thoraeus, K J Vikterlof and R Walstam Kilocurie cobalt 60 therapy at the Radiumhemmet Equipment, technique and dose measurements 1959 *Price Sw Kr 35*
180 Bengt Lilja Motor activity of the stomach 1959 *Price Sw Kr 25*
181 Per Amundsen The diagnostic value of conventional radiological examination of the heart in adults (Appendix by R G Carpenter An account of the statistical analysis of the relative heart volumes of 755 patients in various disease groups) 1959 *Price Sw Kr 20*
182 H M Truby Acoustico cineradiographic analysis considerations with especial reference to certain consonantal complexes 1959 *Price Sw Kr 35*
183 Erik Boijsen Angiographic studies of the anatomy of single and multiple renal arteries 1959 *Price Sw Kr 30*
184 Gustaf Notter A technique for destruction of the hypophysis using Y^{90} spheres A radiologic endocrine and histologic study 1959 *Price Sw Kr 35*
185 Bengt Liliequist The subarachnoid cisterns An anatomic and roentgenologic study 1959 *Price Sw Kr 35*
186 Bengt Liliequist Pontine angle tumour Encephalographic appearances 1959 *Price Sw Kr 30*
187 Holger Skoldborn On the design physical properties and practical application of small condenser ionization chambers 1959 *Price Sw Kr 30*
188 Jens Nielsen Anno Aetatis Suae LX Papers dedicated to Jens Nielsen professor of radiotherapy at the University of Copenhagen on his sixtieth anniversary December 19 1959 *Price Sw Kr 40*

189 OLOV DAHL and KARL JOHAN VIKTERLOF Attainment and value of precision in deep radiotherapy Some fundamentals with special reference to moving beam therapy with 200 to 250 kV roentgen rays and cobalt 60 gamma radiation 1960 *Price Sw Kr 35*

190 RUNE SOREMARK Distribution and kinetics of bromide ions in the mammalian body Some experimental investigations using Br[80m] and Br[82] 1960 *Price Sw Kr 30*

191 ULF BORELL and INGMAR FERNSTRÖM Radiologic pelvimetry 1960 *Price Sw Kr 30*

192 NILS LINDVALL Renal papillary necrosis A roentgenographic study of 155 cases 1960 **(Out of print)**

193 PAUL EDHOLM The tomogram Its formation and content 1960 *Price Sw Kr 30*

194 RAINO KIVILUOTO Pleural calcification as a roentgenologic sign of non-occupational endemic anthophyllite asbestosis (Mineralogic appendix by OLAVI KLOVO) 1960 *Price Sw Kr 25*

195 SVEN SCHELLER Roentgenographic studies on epiphysial growth and ossification in the knee 1960 *Price Sw Kr 35*

196 K A HULTBORN and BO TORNBERG Mammary carcinoma The biologic character of mammary carcinoma studied in 517 cases by a new form of malignancy grading 1960 *Price Sw Kr 35*

197 LARS R HOLSTI The mitotic and radioprotective effect of cysteine and lysine in rat 1960 *Price Sw Kr 30*

198 OSBORNE BARTLEY The isometric relaxation phase of the left ventricle An electrokymographic study 1960 *Price Sw Kr 35*

199 GUNNAR WILLER VESTBY Vaso-seminal vesiculography in hypertrophy and carcinoma of the prostate with special reference to the ejaculatory ducts 1960 *Price Sw Kr 35*

200 BJORN NORDENSTROM Contrast examination of the cardiovascular system during increased intrabronchial pressure 1960 *Price Sw Kr 30*

201 GIOVANNI DI CHIRO RISA encephalography and conventional neuroradiologic methods A comparative study 1961 *Price Sw Kr 35*

202 LARS BJORK Velopharyngeal function in connected speech Studies using tomography and cineradiography synchronized with speech spectrography 1961 *Price Sw Kr 25*

203 BENGT O NYLEN Cleft palate and speech A surgical study including observations on velopharyngeal closure during connected speech using synchronized cineradiography and sound spectrography 1961 *Price Sw Kr 25*

204 S R KJELLBERG B NORDENSTROM U RUDHE V O BJORK and G MALMSTRÖM Cardioangiographic studies of the mitral and aortic valves 1961 *Price Sw Kr 30*

205 GUNNAR CARLBERGER Kinetics and distribution of radioactive cobalt administered to the mammalian body 1961 *Price Sw Kr 30*

206 HANS MOELL Kidney size and its deviation from normal in acute renal failure A roentgendiagnostic study 1961 *Price Sw Kr 25*

207 LEIF KULD HANSEN Micturition cystourethrography with automatic serial exposures An opinion on the value of the method 1961 *Price Sw Kr 30*

208 FINN LUNDWALL Cancer of the vulva A clinical review 1961 *Price Sw Kr 30*

209 ILMARI LINDGREN Anatomical and roentgenologic studies of tuberculous infections in BBC-vaccinated and non vaccinated subjects with biophysical investigations of calcified foci 1961 *Price Sw Kr 25*

210 PER ERIK E BERGNER The significance of certain tracer kinetical methods especially with respect to the tracer dynamic definition of metabolic turnover 1962 *Price Sw Kr* 30

211 P VUORINEN P ANTTILA U WEGELIUS A KAUPPILA and E KOIVISTO Renal cortical index and other roentgenographic renal measurements 1962 *Price Sw Kr 25*

List of Supplements to Acta Radiologica

Nos 173—312

(Issued December 1971)

For Suppl Nos 1—172 inclusive see list issued December 1960 in Vol 54 fasc 6

The supplements are published from time to time and are not included in the subscription rate Prices and year of publication of numbers already issued are detailed below

173 Erik Odeblad Bjorn Westin and Sven Erik Englund Disappearance measurements Theoretical, technical biological and medical aspects 1959 *Price Sw Kr 30*

174 Lars Billing and Erik Severin Slipping epiphysis of the hip A roentgenological and clinical study based on a new roentgen technique 1959 *Price Sw Kr 35*

175 Åke Hanngren Studies on the distribution and fate of C^{14} and T labelled p amino salicylic acid (PAS) in the body 1959 *Price Sw Kr 25*

176 Lars Bjork Cineradiographic studies on the Fallopian tubes in rabbits 1959 *Price Sw Kr 25*

177 Pekka Vuorinen The roentgenographic slit methods A survey and analysis of procedures based on the use of a narrow bundle of roentgen rays (scanography) 1959 *Price Sw Kr 25*

178 Bengt H O Rosengren Determination of cell mass by direct X ray absorption 1959 *Price Sw Kr 25*

179 S Hultberg O Dahl R Thoraeus, K J Vikterlof and R Walstam Kilocurie cobalt 60 therapy at the Radiumhemmet Equipment technique and dose measurements 1959 *Price Sw Kr 35*

180 Bengt Lilja Motor activity of the stomach 1959 *Price Sw Kr 25*

181 Per Amundsen The diagnostic value of conventional radiological examination of the heart in adults (Appendix by R G Carpenter An account of the statistical analysis *of the relative heart volumes of 755 patients in various disease groups*) 1959 *Price Sw Kr 20*

182 H M Truby Acoustico cineradiographic analysis considerations with especial reference to certain consonantal complexes 1959 *Price Sw Kr 35*

183 Erik Boijsen Angiographic studies of the anatomy of single and multiple renal arteries 1959 *Price Sw Kr 30*

184 Gustaf Notter A technique for destruction of the hypophysis using Y^{90} spheres A radiologic endocrine and histologic study 1959 *Price Sw Kr 35*

185 Bengt Liliequist The subarachnoid cisterns An anatomic and roentgenologic study 1959 *Price Sw Kr 35*

186 Bengt Liliequist Pontine angle tumour Encephalographic appearances 1959 *Price Sw Kr 30*

187 Holger Skoldborn On the design physical properties and practical application of small condenser ionization chambers 1959 *Price Sw Kr 30*

188 Jens Nielsen Anno Aetatis Suae LX Papers dedicated to Jens Nielsen professor of radiotherapy at the University of Copenhagen *on his sixtieth anniversary* December 19 1959 *Price Sw Kr 40*

235 ANDERS LUNDERQUIST Angiography in carcinoma of the pancreas 1965 *Price Sw Kr 35*
236 RUNE WALSTAM Studies on therapeutic short-distance and intracavitary gamma beam techniques — Physical considerations with special reference to radiation protection 1965 (Out of print)
237 KAI SETALA Differences in pharmacodynamic response to colchicine between benign and malignant epidermal hyperplasias — An experimental study in skin tumor resistant mice 1965 *Price Sw Kr 30*
238 UNO ERIKSON Circulation in traumatic amputation stumps — An angiographical and physiological investigation 1965 *Price Sw Kr 35*
239 CARL GUSTAF STANDERTSKJOLD-NORDENSTAM The pulmonary circulation during pneumonia — A cinedensigraphic study 1965 *Price Sw Kr 35*
240 ANTTI CEDERBERG Granulocyte distribution in bone marrow blood and different organs in whole body irradiated rats 1965 *Price Sw Kr 35*
241 KAI SETALA Decorporation of radiostrontium Radioactive assay techniques — An experimental study on mice 1965 *Price Sw Kr 30*
242 SHINJI TAKAHASHI Conformation radiotherapy — Rotation techniques as applied to radiography and radiotherapy of cancer 1965 *Price Sw Kr 40*
243 J TH VAN DER WERFF Radioactive bismuth [206] Bi — Experimental studies and clinical applications 1965 *Price Sw Kr 35*
244 SAMUEL S KUROHARA Effects of ionizing radiation on creatine metabolism in patients treated for malignancy and in rats 1965 *Price Sw Kr 35*
245 PER WESTLING Studies of the prognosis in Hodgkin s disease 1965 *Price Sw Kr 35*
246 SVEN GOTTMAR ERICSSON Quantitative microradiography of cementum and abraded dentine — A methodological and biological study 1965 *Price Sw Kr 35*
247 MAURI WILJASALO Lymphographic differential diagnosis of neoplastic diseases 1965 *Price Sw Kr 35*
248 SVEN SCHELLER Roentgenographic studies on the ossification of the distal femoral epiphysis 1965 *Price Sw Kr 30*
249 ROAR NISSEN MEYER Castration as part of the primary treatment for operable female breast cancer — A statistical evaluation of clinical results 1965 *Price Sw Kr 35*
250 ELIS BERVEN SVEN HULTBERG HANS LUDVIG-KOTTMEIER ROLF SIEVERT LARS SANTESSON and BENGT SYLVEN The first fifty years Radiumhemmet 1910—1937 and King Gustaf V Jubilee Clinic 1938—1960 1965 *Price Sw Kr 30*
251 MATS HAVERLING Renal phlebography — An experimental study in the pig 1966 *Price Sw Kr 30*
252 GUNNAR WESTBERG Gas myelography and percutaneous puncture in the diagnosis of spinal cord cysts 1966 *Price Sw Kr 30*
253 SVEN IVAR SELDINGER Percutaneous transhepatic cholangiography 1966 *Price Sw Kr 35*
254 FIRST NORDIC RADIATION PROTECTION CONFERENCE Proceedings Stockholm 1966 Edited by K Lidén and Erik Lindgren *Price Sw Kr 35*
255 LAWRENCE JOSEPH VAN C RA Application of digital computers in radiation dosimetry 1966 *Price Sw Kr 35*
256 HANS LUDIN Aortography Fluid dynamics and technical problems 1966 *Price Sw Kr 35*
257 HJALMAR BOLIN Contrast medium in kidney during angiography — A densitometric method for estimation of renal function 1966 *Price Sw Kr 30*

212 LARS ANDREN Pelvic instability in newborns with special reference to congenital dislocation of the hip and hormonal factors A roentgenologic study 1962 *Price Sw Kr 30*

213 NILS MAGNUS OHLSSON Left heart and aortic blood flow in the dog Precision motion analysis of high speed (270 frames/sec) cinefluorographic recordings 1962 *Price Sw Kr 35*

214 BENGT TJERNBERG Lymphography An animal study on the diagnosis of V × 2 carcinoma and inflammation 1962 *Price Sw Kr 35*

215 PAAVO KLAMI Periarthrosis calcarea of the shoulder joint Its differentiation from other stiff and painful shoulders 1962 *Price Sw Kr 30*

216 P EDHOLM I FERNSTROM K LINDBLOM and S I SELDINGER Roentgen television in practice with special regard to puncture examinations 1962 *Price Sw Kr 35*

217 FOLKE EDSMYR Carcinoma of the vulva An analysis of 560 patients with histologically verified squamous cell carcinoma 1962 *Price Sw Kr 30*

218 P SOILA, M GRONROOS O KAUPPILA und L PYYKONEN Wasserlosliche, viskosierte wasserlosliche und jodolige Kontrastmittel in der Hysterosalpingographie Vergleichende Untersuchungen 1962 *Price Sw Kr 25*

219 STIG SANDMARK Hiatal incompetence Studies on mechanics and principles of examination for hiatus hernia and gastro oesophageal reflux 1963 *Price Sw Kr 25*

220 MAX LUNDBERG Free movements in the temporomandibular joint A cineradiographic study 1963 *Price Sw Kr 30*

221 ÅKE NORHAGEN Selective angiography of the hepatic veins Experimental investigations of basal circulatory dynamics 1963 *Price Sw Kr 35*

222 ERLING HAMMER JACOBSEN Genetically significant radiation doses in diagnostic radiology 1963 *Price Sw Kr 35*

223 ASTRID BROHULT Alkoxyglycerols and their use in radiation treatment An experimental and clinical study 1963 *Price Sw Kr 30*

224 CARL OLOF OVENFORS Pulmonary interstitial emphysema — An experimental roentgen diagnostic study 1964 *Price Sw Kr 35*

225 GEORG THEANDER *Variation in shape of gallbladder during cholecystography* 1964 *Price Sw Kr 30*

226 HUGO BOGREN The composition and structure of human gallstones 1964 *Price Sw Kr 30*

227 LARS NORDQVIST The sagittal diameter of the spinal cord and subarachnoid space in different age groups — A roentgenographic post mortem study 1964 *Price Sw Kr 25*

228 LENNART WICTORIN Bone resorption in cases with complete upper denture — A quantitative roentgenographic photogrammetric study 1964 *Price Sw Kr 30*

229 ARNFINN ENGESET Irradiation of lymph nodes and vessels — Experiments in rats with reference to cancer therapy 1964 *Price Sw Kr 30*

230 LARS HOLLENDER Determining the elements of the interior orientation in roentgenography 1964 *Price Sw Kr 30*

231 HANS HENRIK HOLM The hydrodynamics of micturition — Examination by means of micro manometer and uroflowmeter of the hydrodynamic conditions in normal subjects and in patients suffering from obstruction in the posterior part of the urethra 1964 *Price Sw Kr 30*

232 EBBE CEDERQUIST Clinical application of whole body counting of ^{85}Sr and ^{47}Ca in patients with and without widespread malignant skeletal disease 1964 *Price Sw Kr 30*

233 SVEN PAULIN Coronary angiography — A technical anatomic and clinical study 1964 *Price Sw Kr 40*

234 TROFLS MUNKNER The influence of para aminosalicylic acid on the I ^{131} metabolism 1965 *Price Sw Kr 30*

ACTA RADIOLOGICA

OFFICIAL ORGAN OF THE RADIOLOGICAL SOCIETIES OF
DENMARK FINLAND NORWAY AND SWEDEN

Vol 10 Fasc 1	THERAPY PHYSICS BIOLOGY	1971 February

REMARKS ON THE THEORY OF ENERGY DEPOSITION IN CAVITIES

by

L V Spencer

I wish to discuss energy dissipation in cavities today relating what I say at appropriate points to work by Louis Harold Gray on this subject

It was not my privilege to be personally acquainted with Dr Gray, but in reading of his life and work I have been impressed with the broad range of his scientific interests — from nuclear physics to biology, including both experimental and theoretical work, and combining intensive individual research with group leadership and administrative responsibilities (Loutit & Scott 1966) In addition he was a deeply dedicated human being in activities outside the laboratory It is a pleasure and a rare privilege to pay tribute to him today in recognition of one part of his technical contributions

Attendance at this congress has made it possible for me to get acquainted with many friends of Gray s In addition to their affection and high regard for him there clearly exist other bonds of mutual support and encouragement extending across national boundaries and making a happy adventure out of the difficult research problems I wish my salute to Gray to include the many people who have shared in Gray's accomplishments through these bonds of association

---

From the National Bureau of Standards Washington D C U S A This article was given as the ICRU Gray Medal Lecture on October 10 1969 at the XIIth Internat Congr Radiology Submitted for publication 14 April 1970

these quantities are called the initial values or conditions Particles can appear in the cavity either by emergence through the cavity surface or by some interaction which produces them at an internal position The initial conditions are stated in the same way for both cases

Two simple ideas have dominated the use of cavities as measurement probes by making the cavity very small one aims to sample conditions in the medium without creating a disturbance which obscures the interpretation of the measurement Or by making the material in the cavity equivalent to that of the medium one can both eliminate any disturbance, and sample conditions more certainly

I will refer to the case in which the cavity material differs from the wall material only in regard to density as the 'homogeneous case A formal proof was given about 15 years ago by FANO (1954) that if a radiation source is at all points proportional to density, the resulting flux of the radiation has at all points the same intensity the same spectrum, and the same angular distribution independently of the density (Due to density dependence of cross sections for electron interactions this theorem does not hold rigorously, and it breaks down seriously for electrons with kinetic energy above a few MeV) We call this Fano s theorem because he first proved it and it justifies efforts to achieve the homogeneous case in the construction of detectors I will mention both the homogeneous case and Fano s theorem a number of times

Historical In GRAY s classic paper (1936) he refers to another paper of his which was published 8 years previously (1928) when he was about 23 years old and he also mentions Sir William Bragg s book Studies in Radioactivity published in 1912 The question of comparative contributions by BRAGG and GRAY to the 'Bragg Gray principle has often come up in conversations I would like to review this early work because I have never read a fully satisfactory summary of it

Ionization of gases was very early identified as one of the *properties of* roentgen rays and of radiations produced by naturally radioactive materials BRAGG s *1912* book is a study of the physical properties of α β and γ rays, with emphasis on their use to investigate the structure of matter The book was published a *year or so* after Rutherford s nuclear hypothesis and before Bohr s work on classical stopping power theory but *the contents* summarize the major penetration phenomena of these radiations with *great insight*

BRAGG was well aware of the main stopping power and range phenomena of heavy charged particles and it was his *assumption that* electrons behaved similarly except for the ease with which they *were deflected Hence* if their paths could be straightened out one would expect *corresponding* concepts of range and stopping power to be applicable It was to obtain information on

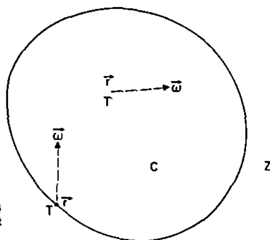


Fig 1 Initial parameters for particles which (1) enter through the cavity interface or (2) start their trajectory at an internal point

This lecture will be oriented more towards a better understanding of the technical developments of the past than towards development of new theory So I wish to warn you beforehand not to expect much in the way of new concepts or data

Fig 1 identifies a cavity surrounded by a medium The symbols Z, and C, refer generically to the material comprising the medium and the cavity, respectively From the point of view of radiation measurement, the cavity can be considered a probe, and there is the fundamental problem of relating measurements performed with this probe to quantities of interest in the medium The material in the cavity can be identical with that of the medium, or it can be of higher or lower atomic number It can be solid, liquid, or gas The measurement can be of ions formed, light emitted, or other physical quantities The cavity can be large or small, though more interest in the past has been focused on small cavities Cavity shape is arbitrary, although convexity has been the rule, and more interest has been centered on spherical, cylindrical, and plane layer shapes Cavities used as probes appear in measurement problems for many types of radiation, although the discussion here will be limited to fast electrons Finally, although many different radiation effects are of interest, the elementary problem of energy deposition in the cavity is the central one in this discussion

Thus the simple cavity problem has a generality which is not immediately obvious And the apparent simplicity quickly vanishes on closer inspection For future reference, let us name the kinetic energy T, the position vector $\vec{r}$, and the direction of travel $\vec{\omega}$ When a particle is first introduced into the cavity,

through the walls, with no concern given to previous trajectory, and (2) electrons born in the cavity gas We will refer to the first as the surface contribution because the cavity interface is relevant, and we will call the second the source contribution even though, from the point of view of the cavity both are sources For electrons of either class GRAY considered the particle trajectory after re entry into the walls to be irrelevant and he therefore focused attention on energy deposition for single traversals

GRAY s main argument used a comparison of the cavity with a similarly shaped volume of the wall material just large enough to cause the same energy loss when traversed by a fast electron With this comparison he argued that the surface contribution must be proportional to the photon energy absorbed per gram of wall material Then assuming the cavity to be small (i e containing little material) so that the source contribution was much smaller than the surface contribution he equated the source contribution to that in the comparison volume of wall material which must likewise be proportional to the energy input by photons into the wall material

Supplementing this discussion based on single traversals of the cavity, GRAY considered the effect of the cavity on the spectrum of fast electrons entering the cavity He first argued that the cavity could modify only that component which re entered after one or more previous traversals From his basic comparison with a volume of wall material, he argued that the energy of electrons re entering the wall after their traversal of the cavity would not be affected by the cavity And by assuming no significant deflection of the electrons in the cavity due to the small amount of material traversed, he argued that angular distributions after traversal of the cavity should also be unaffected

Thus BRAGG and GRAY found ionization in small cavities to be proportional respectively to electron range and to photon energy absorbed per gram of wall material Both argued against any significant disturbance by the cavity of the spectrum of electrons incident on, or within the cavity BRAGG did not discuss his proportionality constant quantitatively and GRAY did not call his proportionality constant the stopping power ratio although this is what he described (Possibly the term stopping power was not yet commonly applied to electrons)

GRAY s argument used assumptions not made by BRAGG e g that electron track segments in the cavity can be assumed to be straight These make possible a quantitative analysis not attempted by BRAGG Unlike BRAGG GRAY did not give special attention to the homogeneous case and I think this is unfortunate because it seems to me that his discussion of the non perturbing effect of a cavity could possibly have been applied to yield a proof of Fano s theorem

GRAY s second paper on the subject published in 1936 begins with an admission that he had overlooked BRAGG s earlier work and an apology for his

electron ranges in different materials that he considered the properties of cavities. His argument was based on the constancy of the product of electron source strength (number/g/s, say) with the total track length (or range) of the electrons (in g/cm², say), when the source is uniformly distributed in the medium; today we would identify this product as the total flux of the electrons. First, he established that a cavity which contained no matter would have no effect on the flux in the surrounding medium, and that the flux would be the same in the cavity as in the wall material. It is quite clear in this discussion that he understands very well the principle of the homogeneous case. In fact he says the following (p. 166): "The density of β rays inside a material of uniform composition traversed by X rays uniformly distributed throughout it depends only on the characteristics of the radiation and the nature of the material, it is independent of the density of the material and has even same value where there is a cavity." This is precisely Fano's theorem as it applies to electron density. But despite the clear enunciation of the principle, BRAGG's discussion does not seem to constitute a proof of the principle.

Having established that the 'density' of fast electrons in a cavity containing no matter would be representative of the density inside the medium, BRAGG considers small cavities containing a bit of air. He states that if the cavity is small, and the surrounding material not too different from air, the cavity would create no disturbance in the electron density, and each volume element of air would contribute ionization accordingly. The total ionization in the air would be proportional to the product of electron source strength times range of the electrons. Hence, if in two media the source strengths were the same, the proportionality constant would be a relative measure of the track lengths of individual electrons in the two media. BRAGG did not carry the analysis to the point of a specific functional dependence of this proportionality constant on the atomic number of cavity or wall materials although he discussed general trends for experimental results and showed that they were qualitatively consistent with the stopping power data for α particles.

GRAY's 1928 paper was likewise mainly oriented towards nuclear physics, in particular the nature of cosmic radiation. The Klein-Nishina formula had recently been published, and GRAY wished to use it in connection with ionization chamber data on cosmic ray absorption, to infer source energies for cosmic rays, under the assumption that they were high energy photons. In this paper the cavity ionization problem was carefully studied.

Stating at the outset that the detailed geometry of the phenomenon was extremely complicated, and that he wished to adopt a simple point of view which would nevertheless permit analysis, GRAY proceeded to divide sources for the cavity ionization into two components: (1) electrons entering the cavity

through the walls, with no concern given to previous trajectory, and (2) electrons born in the cavity gas We will refer to the first as the surface contribution because the cavity interface is relevant and we will call the second the source contribution even though from the point of view of the cavity, both are sources For electrons of either class, GRAY considered the particle trajectory after re entry into the walls to be irrelevant and he therefore focused attention on energy deposition for single traversals

GRAY s main argument used a comparison of the cavity with a similarly shaped volume of the wall material just large enough to cause the same energy loss when traversed by a fast electron With this comparison he argued that the surface contribution must be proportional to the photon energy absorbed per gram of wall material Then assuming the cavity to be small (i e containing little material) so that the source contribution was much smaller than the surface contribution he equated the source contribution to that in the comparison volume of wall material, which must likewise be proportional to the energy input by photons into the wall material

Supplementing this discussion based on single traversals of the cavity, GRAY considered the effect of the cavity on the spectrum of fast electrons entering the cavity He first argued that the cavity could modify only that component which re entered after one or more previous traversals From his basic comparison with a volume of wall material he argued that the energy of electrons re entering the wall after their traversal of the cavity would not be affected by the cavity And by assuming no significant deflection of the electrons in the cavity due to the small amount of material traversed he argued that angular distributions after traversal of the cavity should also be unaffected

Thus BRAGG and GRAY found ionization in small cavities to be proportional respectively to electron range and to photon energy absorbed per gram of wall material Both argued against any significant disturbance by the cavity of the spectrum of electrons incident on or within the cavity BRAGG did not discuss his proportionality constant quantitatively and GRAY did not call his proportionality constant the stopping power ratio, although this is what he described (Possibly the term stopping power was not yet commonly applied to electrons)

GRAY s argument used assumptions not made by BRAGG e g that electron track segments in the cavity can be assumed to be straight These make possible a quantitative analysis not attempted by BRAGG Unlike BRAGG GRAY did not give special attention to the homogeneous case and I think this is unfortunate, because it seems to me that his discussion of the non perturbing effect of a cavity could possibly have been applied to yield a proof of Fano s theorem

GRAY s second paper on the subject published in 1936 begins with an admission that he had overlooked BRAGG s earlier work and an apology for his

electron ranges in different materials that he considered the properties of cavities. His argument was based on the constancy of the product of electron source strength (number/g/s, say) with the total track length (or range) of the electrons (in g/cm², say), *when the source is uniformly distributed in the medium*: today we would identify this product as the total flux of the electrons. First, he established that a cavity which contained no matter would have no effect on the flux in the surrounding medium, and that the flux would be the same in the cavity as in the wall material. It is quite clear in this discussion that he understands very *well the principle of the homogeneous case. In fact* he says the following (p. 166): "The density of β rays inside a material of uniform composition traversed by x rays uniformly distributed throughout it depends only on the characteristics of the radiation and the nature of the material, it is independent of the density of the material and has even same value where there is a cavity". *This is precisely Fano's theorem as it applies to electron* density. But despite the clear enunciation of the principle, BRAGG's discussion does not seem to constitute a proof of the principle.

Having established that the 'density' of fast electrons in a cavity containing no matter would be representative of the density inside the medium, BRAGG considers *small cavities containing a bit of air*. He *states that* if the cavity is small, and the surrounding material not too different from air, the cavity would create no disturbance in the electron density, and each volume element of air would contribute ionization accordingly. The total ionization in the air would be proportional to the product of electron source strength times range of the electrons. Hence, if in two media the source strengths were the same, the proportionality constant would be a relative measure of the track lengths of individual electrons in the two media. BRAGG did not carry the analysis to the point of a specific functional dependence of this proportionality constant on the atomic number of cavity or wall materials although he discussed general trends for experimental results and showed that they were qualitatively consistent with the stopping power data for a particles.

GRAY's 1928 paper was likewise mainly oriented towards nuclear physics, in particular the nature of cosmic radiation. *The Klein-Nishina formula had* recently been published, and GRAY wished to use it in connection with ionization chamber data on cosmic ray absorption, to infer source energies for cosmic rays, under the assumption that they were high energy photons. In this paper the cavity ionization problem was carefully studied.

Stating at the outset that the detailed geometry of the phenomenon was extremely complicated, and that he wished to adopt a simple point of view which would nevertheless permit analysis, GRAY proceeded to divide sources for the cavity ionization into two components: (1) electrons entering the cavity

through the walls, with no concern given to previous trajectory, and (2) electrons born in the cavity gas We will refer to the first as the surface contribution because the cavity interface is relevant, and we will call the second the source contribution even though, from the point of view of the cavity, both are sources For electrons of either class, GRAY considered the particle trajectory after re entry into the walls to be irrelevant, and he therefore focused attention on energy deposition for single traversals

GRAY s main argument used a comparison of the cavity with a similarly shaped volume of the wall material just large enough to cause the same energy loss when traversed by a fast electron With this comparison he argued that the surface contribution must be proportional to the photon energy absorbed per gram of wall material Then assuming the cavity to be small (i e containing little material) so that the source contribution was much smaller than the surface contribution he equated the source contribution to that in the comparison volume of wall material which must likewise be proportional to the energy input by photons into the wall material

Supplementing this discussion based on single traversals of the cavity, GRAY considered the effect of the cavity on the spectrum of fast electrons entering the cavity He first argued that the cavity could modify only that component which re entered after one or more previous traversals From his basic comparison with a volume of wall material, he argued that the energy of electrons re entering the wall after their traversal of the cavity would not be affected by the cavity And by assuming no significant deflection of the electrons in the cavity due to the small amount of material traversed he argued that angular distributions after traversal of the cavity should also be unaffected

Thus BRAGG and GRAY found ionization in small cavities to be proportional, respectively to electron range and to photon energy absorbed per gram of wall material Both argued against any significant disturbance by the cavity of the spectrum of electrons incident on or within the cavity BRAGG did not discuss his proportionality constant quantitatively, and GRAY did not call his proportionality constant the stopping power ratio although this is what he described (Possibly the term stopping power was not yet commonly applied to electrons)

GRAY s argument used assumptions not made by BRAGG, e g that electron track segments in the cavity can be assumed to be straight These make possible a quantitative analysis not attempted by BRAGG Unlike BRAGG, GRAY did not give special attention to the homogeneous case and I think this is unfortunate because it seems to me that his discussion of the non perturbing effect of a cavity could possibly have been applied to yield a proof of Fano s theorem

GRAY s second paper on the subject, published in 1936 begins with an admission that he had overlooked BRAGG s earlier work and an apology for his

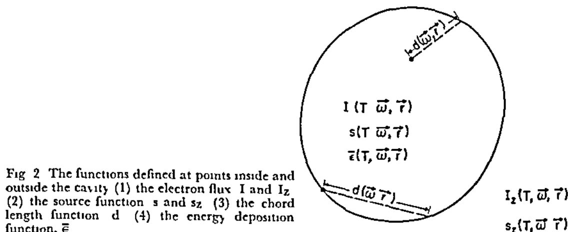


Fig. 2. The functions defined at points inside and outside the cavity: (1) the electron flux I and I_Z; (2) the source function s and s_Z; (3) the chord length function d; (4) the energy deposition function, $\bar{\epsilon}$.

oversight. Incidentally, at the time of that first paper, GRAY was working at the Cavendish laboratory. Furthermore, the paper was sponsored by Lord Rutherford. It is surprising that the discussion in BRAGG's book was apparently not called to his attention by Rutherford, or by others at the laboratory. As I hope to show, however, in addition to the contrast between GRAY's absolute approach, and BRAGG's arguments comparing different wall materials, there were conceptual differences of another type such that it was probably just as well that GRAY's development occurred independently.

Mathematical formulation

At this point, let me begin a more mathematical discussion of the cavity problem. I must apologize that the notation will be my own, and does not make full use of standard terminology.

In Fig. 2 we see the cavity again. The parameters T, $\vec{\omega}$, and $\vec{r}$ still refer to kinetic energy, particle direction, and particle position. The function $d(\vec{\omega}, \vec{r})$ will be called the 'chord length'. Its arguments are the direction and position of a particle at the beginning of its trajectory in the cavity. It measures the length of the straight line segment from $\vec{r}$, extending along $\vec{\omega}$. While the term 'chord' is usually limited to straight line segments which begin and end on the interface, we generalize it to include cases in which the line segment begins internally.

The function $s(T, \vec{\omega}, \vec{r})$ will be called the 'source' function or distribution. It gives the number of electrons generated at points inside the cavity, with initial energy, direction, and position as shown by its arguments.

The electron flux, whose integral may also be referred to as the 'slowing down spectrum', is designated $I(T, \vec{\omega}, \vec{r})$ Here the arguments of the function do not necessarily refer to initial conditions but to kinetic energy and direction o the flux at the position $\vec{r}$ which may be inside or on the surface of the cavity A time dependence for both flux and source can be assumed, but it plays no role, hence the word flux' which I prefer to use, could be replaced by the word fluence

In addition to these quantities there is another function to be introduced, this is $\bar{\epsilon}(T \ \vec{\omega} \ \vec{r})$, which we use to describe the energy deposited or 'dissipated in the cavity We define this function as follows let an electron first appear in the cavity with kinetic energy T, at position $\vec{r}$, and traveling, at first appearance in the cavity, in the direction $\vec{\omega}$ This electron, its secondaries, tertiaries etc and the fluorescence or bremsstrahlung radiation generated in cascade can all exit through the cavity walls The difference between T, and the total energy leaving the cavity constitutes the deposition energy for this electron If an average is performed over a very large number of electrons with identical initial conditions we can obtain the average energy deposition per electron This is what we call $\bar{\epsilon}(T \ \vec{\omega} \ \vec{r})$, with the bar over the ϵ indicating explicitly that the function is an average This function is defined for all points inside the cavity as well as at points on the cavity interface and it is zero if $\vec{\omega}$ does not point into the cavity when $\vec{r}$ is on the interface

Inside the wall material there will be both a particle flux which we designate I_Z and a particle source function designated s_Z, but there will be *no* corresponding energy deposition function or chord length function

In terms of the variables defined, the energy deposited in the cavity per gram of cavity material can be written in the form shown in the following equation

$$E = \frac{1}{V}\int_{4} dO \int_{A} d\sigma \, \vec{\omega} \cdot \vec{n} \int_{0}^{T} dT \, I(T, \vec{\omega}, \vec{r}) \, \bar{\epsilon}\,(T, \vec{\omega}, \vec{r})$$

$$+ \frac{1}{V}\int_{4} dO \int_{V} d\tau \int_{0}^{T} dT \, s\,(T \ \vec{\omega} \ \vec{r}) \, \bar{\epsilon}\,(T \ \vec{\omega} \ \vec{r}) \qquad (1)$$

On the right we have two terms *corresponding* to electrons which enter through the surface and electrons internally generated In the latter, which we call the source term the particles at appearance are weighted with the

energy deposition function to give their contribution, and integration is performed over all spectral energies in the source, all volume elements $d\tau$ in the cavity, and all solid angle elements $d\Omega$. We thus have in the second term the total contribution of the source function to the energy deposited in the cavity. The volume, V, in the denominator, has units which cancel those of $d\tau$, and the source function, s, is given per gram of cavity material, so the units all work out.

In the first, or surface term, the unit vector $\vec{n}$ is the inward normal at the surface element $d\sigma$. Thus the product $\vec{\omega} \cdot \vec{n} I$ is the inward traveling current of particles at $d\sigma$. This is weighted by the energy deposition function $\bar{\epsilon}$, and integration is over the total spectrum, the *complete surface*, and all *directions*. Since the flux, I, incorporates a density factor and is essentially track length per gram, the units of this term also work out.

Interpretation of this equation is clarified somewhat if one notes that in both terms on the right, the integrations are over initial conditions for electrons appearing in the cavity. If we assume that the electrons are generated by photons, and produce additional photons in turn, we would interpret the factors in the cavity equation as follows: one first solves the photon electron cascade transport equations, for medium plus cavity, to obtain the currents of fast electrons and of photons incident with an inward direction at all points on the cavity interface; the inward current of electrons is what we call I. To obtain s we again solve the transport equation but for the photons only, inside the cavity, using the inward photon current as source or boundary condition, and otherwise treating the cavity as if it were surrounded by vacuum. The fast electron producing interactions of the photon flux within the cavity then give rise to s. From this one sees that s *does not include interactions in which* primary electrons generate secondary electrons within the cavity — these are accounted for by $\bar{\epsilon}$.

The energy deposition function is zero at points on the cavity interface, for all directions pointed into the wall. Therefore, that part of the electron flux at the interface moving towards the wall automatically makes no contribution to the integral.

In accordance with GRAY's approach, the flux I takes account of multiple crossings of the cavity interface, while the $\bar{\epsilon}$ takes account only of single crossings. It would be possible to write another equation which looks just the same, but with I taking account of first crossings only, and a function $\bar{\epsilon}$ taking account of multiple crossings. Either approach is general, and both lend themselves to analytical study as well as Monte Carlo computations. The single crossing $\bar{\epsilon}$ applies also to isolated detectors, while the multiple crossing

$\bar{\epsilon}$ would treat re entrant energy as part of the event initiated it Thus both approaches have important areas of special relevance Since we do not have time to discuss both we limit our comments to the single crossing $\bar{\epsilon}$ case which corresponds to GRAY s point of view

As we have already shown, eq (1) can be applied, with appropriate interpretation of the source function, to photon electron cascades It also applies to cavities of all sizes and to non equilibrium situations Nothing about the equation is particularly new, since the $\bar{\epsilon}$ is essentially a response function, with the cavity representing a detector

The form of this equation is similar to that of many equations appearing in say classical electromagnetic theory in that both surface and volume integrals appear This suggests that we might apply Gauss theorem to change the surface integral into a volume integral This can be done and the result is

$$E = \frac{1}{V}\int_{4\pi} d\Omega \int_{V} d\mathbf{r} \int_{0}^{T} dT\{-\nabla\cdot(\vec{\omega} I\bar{\epsilon}) + s\bar{\epsilon}\} \tag{2}$$

Here the arguments of the functions appearing in the integrand have not been written out Although equivalent to eq (1) this equation is not so simply interpreted except that energy deposition is here implicitly a process occurring at all points within the cavity

One can pursue this volume point of view further and I would like to sketch the main points of the argument

The gradient is essentially a derivative and it applies to each factor, producing

$$-\nabla\cdot(\vec{\omega} I\bar{\epsilon}) + s\bar{\epsilon} = -I(\vec{\omega}\cdot\nabla\bar{\epsilon}) + \bar{\epsilon}[-\vec{\omega}\cdot\nabla I + s] \tag{3}$$

Here both sides give the integrand of the cavity integral and all functions and operations are defined at points inside the cavity

The quantity in brackets on the right of eq (3) is the sum of two of the terms for the electron transport equation inside the cavity,

$$-\vec{\omega}\cdot\nabla I + s = -\int_{T}^{T} dT \int_{4\pi} d\Omega\, k(T\,\vec{\omega} \to T'\,\vec{\omega}')\, I(T\,\vec{\omega}, \vec{r}) + \int_{0}^{T} dT' \int_{4\pi} d\Omega'\, k(T'\,\vec{\omega}', T\,\vec{\omega})\, I(T', \vec{\omega}'\,\vec{r}) \tag{4}$$

where k includes secondary electron generation in the first term on the right but not the second We can replace the quantity in brackets with the scattering terms on the right of the transport equation this introduces integrals over energy and direction into (2) in addition to corresponding operations of the

cavity integral. By interchanging the order of integrations, so that those of the scattering term of eq. (4) are taken last, the integrand of the cavity integral can be written so that I appears as a factor which multiplies the terms on the left side of the following equation

$$-\vec{\omega}'\cdot\nabla\bar{\epsilon}(T',\vec{\omega}',\vec{r}) + \int_0^{T} dT \int_{4\pi} d\Omega\; k(T',\vec{\omega}',T,\vec{\omega})\,[\bar{\epsilon}(T',\vec{\omega}',\vec{r})-\bar{\epsilon}(T,\vec{\omega},\vec{r})] = D(T') \tag{5}$$

where $\vec{\omega}'$, T' have replaced $\vec{\omega}$, T as dummy variables in the first two terms, this combination of terms has been designated D in eq. (5), a function which must be a type of stopping power for energy deposition, a basic response function for the material in the cavity. (A point detector of the material would have $D(T')$ as its response function, speaking somewhat loosely.) Function D should ordinarily be independent of position in the cavity, and also independent of direction, so that it has been written in eq. (5) as a function of kinetic energy only.

This equation has a similarity to eq. (4): it is called the 'adjoint equation'. The function D is the source function for this equation, and in principle it is determined by the properties of the material and not the cavity geometry. Once D has been specified, eq. (5) can be solved to determine $\bar{\epsilon}$. The solution progresses backwards in position, as it were, and upwards in energy, and would have as boundary condition at the interface the value $\bar{\epsilon} = 0$, for $\vec{\omega}'$ pointing towards the wall, as already mentioned.

The cavity integral can now be written in two forms. In addition to the form which utilizes $D(T)$

$$E = \frac{1}{V}\int_V d\tau \int_{4\pi} d\Omega \int_0^T dT\, I[D] \tag{6}$$

we rewrite eq. (1) so that analogous features can be better identified

$$E = \frac{1}{V}\int_V d\tau \int_{4\pi} d\Omega \int_0^T dT\, \bar{\epsilon}[\vec{\omega}\cdot\vec{n}I\,|\nabla b|\,\delta(b(\vec{r})) + s] \tag{7}$$

where the points on the cavity interface represent the solutions of $b(\vec{r}) = 0$, and $\vec{n}$ can be identified more generally as the unit vector pointing inward and parallel or anti-parallel to ∇b. Due to the delta function, the first term in brackets in eq. (7) vanishes except at the cavity interface, and represents electrons entering the cavity through the interface.

We should note that in eq (6) the solution to the transport equation I, is multiplied by the source function of the adjoint equation, D, while in eq (7) the solution to the adjoint equation, $\bar{\epsilon}$, is multiplied by the full source of electrons for transport inside the cavity

These two forms illustrate two alternative points of view One may ask what the total contribution is of each group of electrons which enters the cavity This is clearly GRAY s point of view On the other hand, one may ask about the rate at which all electrons, from whatever entry point, contribute to energy deposition through interactions occurring in different volume elements inside the cavity For want of better names I call the former the 'surface approach and the latter the volume approach

I have wondered if this difference did not exist between BRAGG and GRAY that is, if BRAGG did not view the problem as one in which the electron spectrum generates ions on the spot at all points inside the cavity, rather than viewing the problem as one in which a capacity for ion generation is associated with entry into the cavity I find BRAGG s argument fully understandable in terms of volume concepts, since he writes of the electron density in the cavity and of the number of β rays crossing each unit volume of the cavity rather than of the number of β rays entering the cavity Thus the points of view of BRAGG and GRAY appear to be complementary rather than overlapping

This same dichotomy of viewpoints characterizes the later theoretical developments and it is quite possible to arrange Monte Carlo calculations to express either point of view So I think this pair of contrasting approaches will continue to be with us

It will be useful in discussing later theoretical developments, to consider GRAY's calculation once more, as an approximate procedure for evaluating the cavity integral One assumes that energy which is transferred from primary to secondary electrons through interactions occurring within the cavity will remain in the cavity and that this is a continuous process This leads to introduction of the concept of stopping power Next one assumes that the cavity is small so that s is of negligible importance This same assumption encourages one to say also that path segments are straight in the cavity because the cavity then appears very thin to most electrons

With these assumptions and for unit source strength the I which now refers to primaries only is quite accurately equal to the reciprocal of the stopping power for the wall material And the $\bar{\epsilon}$ can be approximated by the product of the stopping power for the cavity material and the chord length Then the integrals over direction and position on the interface can be performed, and one arrives at expressions for the mean stopping power ratio which have been

the subject of many computations, and which one calls the Bragg Gray principle.

The main mathematical connection between the I and its adjoint, the $\bar{\epsilon}$, comes at the point of ensuring that energy is assigned either to deposition, or to the spectrum, but not to both. *Energy conservation must be observed*, and this requirement appears most clearly for the homogeneous case. One must use forms for the I and the $\bar{\epsilon}$ such that in the homogeneous case the integrals give back the known energy input. This happens, *of course, with the approximate* forms just identified as giving the Bragg Gray result.

Beyond this the mathematical connection between I and $\bar{\epsilon}$ is not very tight. In *some linear systems it is possible to identify a simple transformation which* makes it possible to generate one of the two adjoint functions conveniently from the other. This does not seem to be the case here. What one can do I think is apply *variational techniques* (SELENGUT 1958, O'REILLY 1968). I expect these to be a source of new analytic or semi analytic developments. In fact, I believe that the data produced beginning about 1955 can be viewed as result*ing from a type of variational calculation*.

More recent developments

I wish to turn now to a brief discussion of some of the main theoretical developments which go beyond the elementary stopping power ratio.

We have just seen that GRAY*'s approach is equivalent to approximation* of $\bar{\epsilon}$ with the product of stopping power and chord length. In 1955, BURCH published a discussion of the problem in which he observed that the chord length *should be replaced by a mean track length in the cavity*, which would include detours. Further, the stopping power should be reduced by omission of that part of the energy of secondary electrons which leaves the cavity, and, corre*spondingly, the inward bound spectrum* of electrons should include secondary electrons. At the time (1955), the computational machinery for making these changes did not happen to be available, so that it wasn't feasible to carry out such a program. This machinery is available now, and I think it is still a good idea to express the $\bar{\epsilon}$ in a fashion that puts most of the geometric complexity into a mean path length for the cavity.

Concurrently with BURCH, in 1955, ATTIX and I (SPENCER & ATTIX) took the other (volume) point of view and tried somewhat intuitively to express things in terms of a suitable energy deposition function which incorporates some information about the cavity geometry. I wish to show how this approach can be formally developed as an approximate evaluation of the cavity integral.

Please recall that the D in the volume form of the cavity integral should,

strictly speaking include only those interactions which remove energy permanently from the spectrum of moving electrons In practice however calculations feasible today will always use a cut off at low energies, which we will call δ so that slow electrons as well as excitations represent part of the dissipated energy The cut off would be set at a very low value, so that distances of electron travel are always negligible in comparison with cavity sizes With or without this convention D is a property of the material not expressing in any way the cavity geometry and large contributions to the cavity integral in eq (6) could therefore be expected from low energy spectral regions that are not well known

Attix and I got around this problem as follows first, we limited our discussion to small cavities so that one does not have to give special consideration to the source term In addition for small cavities it is not unreasonable to consider that at all points in the cavity one sees the same spectrum Note that this is a more drastic assumption than Gray s—we are now talking not about the spectrum which enters but about the spectrum at inner points, we assume that it is independent of position inside the cavity This fundamental assumption has two consequences first it removes the grad I term from the integrand as written in eq (3) on the right and secondly because the I is independent of position the space integration applies directly to the grad $\bar{\epsilon}$ factor in the remaining term What one has with performance of the integration over space is a space average of the grad $\bar{\epsilon}$ term for each direction $\vec{\omega}$ We perform this space average not on the gradient term directly but on the terms from the adjoint equation which equal the directional derivative factor $\vec{\omega}\,\nabla\bar{\epsilon}$ This integration does not affect the source term of the adjoint equation but it replaces $\bar{\epsilon}\,(T\ \vec{\omega}\ \vec{r})$ by an average value for all positions in the cavity as shown in the following expression

$$\frac{1}{\mathrm{V}}\int_V d\tau\, I(T\ \vec{\omega})\,\{-\vec{\omega}\ \nabla\bar{\epsilon}\}$$

$$= I(T\ \vec{\omega})\left\{\int_4 d\Omega\int_\delta^T dT\,k(T\ \vec{\omega}\ T\ \vec{\omega})\left[\frac{1}{\mathrm{V}}\int_V d\tau\,\bar{\epsilon}\,(T,\vec{\omega}\ \vec{r})\right.\right. \tag{8}$$

$$\left.\left.-\frac{1}{\mathrm{V}}\int_V d\tau\,\bar{\epsilon}\,(T\ \vec{\omega},\vec{r})\right] + D(T)\right\}$$

where δ is the cut off which distinguishes dissipative from non dissipative interactions

the subject of many computations, and which one calls the Bragg-Gray principle.

The main mathematical connection between the I and its adjoint, the $\bar{\epsilon}$, comes at the point of ensuring that energy is assigned either to deposition, or to the spectrum, but not to both. Energy conservation must be observed and this requirement appears most clearly for the homogeneous case. One must use forms for the I and the $\bar{\epsilon}$ such that in the homogeneous case the integrals give back the known energy input. This happens, of course, with the approximate forms just identified as giving the Bragg-Gray result.

Beyond this the mathematical connection between I and $\bar{\epsilon}$ is not very tight. In some linear systems it is possible to identify a simple transformation which makes it possible to generate one of the two adjoint functions conveniently from the other. This does not seem to be the case here. What one can do I think is apply variational techniques (SELENGUT 1958, O'REILLY 1968). I expect these to be a source of new analytic or semi-analytic developments. In fact, I believe that the data produced beginning about 1955 can be viewed as resulting from a type of variational calculation.

More recent developments

I wish to turn now to a brief discussion of some of the main theoretical developments which go beyond the elementary stopping power ratio.

We have just seen that GRAY's approach is equivalent to approximation of $\bar{\epsilon}$ with the product of stopping power and chord length. In 1955, BURCH published a discussion of the problem in which he observed that the chord length should be replaced by a mean track length in the cavity, which would include detours. Further, the stopping power should be reduced by omission of that part of the energy of secondary electrons which leaves the cavity, and, correspondingly, the inward bound spectrum of electrons should include secondary electrons. At the time (1955), the computational machinery for making these changes did not happen to be available, so that it wasn't feasible to carry out such a program. This machinery is available now, and I think it is still a good idea to express the $\bar{\epsilon}$ in a fashion that puts most of the geometric complexity into a mean path length for the cavity.

Concurrently with BURCH, in 1955, ATTIX and I (SPENCER & ATTIX) took the other (volume) point of view and tried somewhat intuitively to express things in terms of a suitable energy deposition function which incorporates some information about the cavity geometry. I wish to show how this approach can be formally developed as an approximate evaluation of the cavity integral.

Please recall that the D in the volume form of the cavity integral should,

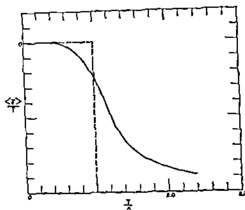


Fig 3 Solid line the fraction of the kinetic energy deposited in a spherical cavity as a function of electron kinetic energy dashed line step function approximation used in computations

where $\langle\bar{\epsilon}\rangle/T$ is the fraction of the secondary electron energy which the secondary leaves in the cavity on the average The first term on the right of eq (11) adjusts the energy deposition by primaries to take account of corresponding energy losses

We have not yet stated assumptions about I and $\langle\bar{\epsilon}\rangle$ which are appropriate for calculations for the I we use the slowing down spectrum for the homogeneous wall case For the $\langle\bar{\epsilon}\rangle$ we use the crude assumption that this equals the electron kinetic energy below a cut off energy Δ and vanishes above this cut off The value of Δ is chosen according to the size of the cavity, and would be at much higher energies than the other cut-off, δ, used in determination of D

The calculation of $\bar{S}$ can proceed, with these assumptions It yields exactly the limited stopping power function which ATTIX and I used in our 1955 paper, including the feature of vanishing below Δ

A word needs to be said in justification of the I approximation and the even more arbitrary $\langle\bar{\epsilon}\rangle$ which have been inserted into eqs (11) and (11) First it should be observed that this choice conserves energy in the homogeneous case if the cross sections used for the calculation of $\bar{S}$ are those also used to determine I Secondly at high energies one expects I to be little affected by the presence of the cavity The main effect of the cavity on the spectrum occurs in a band of kinetic energies for which the electron has a range a little greater or a little less than the diameter of the cavity There would be secondary electrons produced with energies in this band as well as electrons which enter the band from higher energies The component which exhibits the main changes due to the presence of the cavity has moved from higher energies, spending part of its

We assume that the scattering kernel is a function of $\vec{\omega}' \cdot \vec{\omega}$, and represent it as a Legendre series, this leads to a sum of spherical harmonics coefficients

$$\int_{4\pi} d\Omega \frac{1}{V}\int_{V} d\tau\, I(T', \vec{\omega}')\{-\vec{\omega} \cdot \nabla \bar{\epsilon}\} = \sum_{l=0}^{\infty}\sum_{m=-l}^{l} \frac{2l+1}{4\pi} I_l^m(T') \int_{0}^{T'} dT\,[k_l^0(T', T)\,\bar{\epsilon}_l^m(T) - k_0^0(T', T)\bar{\epsilon}_l^m(T')] + I_0(T')\,D(T') \qquad (9)$$

where, for example, (see ref. 9 for definitions of the $\mathcal{Y}_l^m$ and its complex conjugate, $\bar{\mathcal{Y}}_l^m$)

$$\bar{\epsilon}_l^m(T) = \sqrt{\frac{4\pi}{2l+1}}\int_{4\pi} d\Omega\, \bar{\mathcal{Y}}_l^m(\vec{\omega})\left[\frac{1}{V}\int_{V} d\tau\, \bar{\epsilon}(T, \vec{\omega}, \vec{r})\right] \qquad (9')$$

Now, we do not expect spatial cavity averages of the energy deposition function to depend much on the direction — for spherical cavities there should be no dependence whatever. Further, at low energy, one expects I to be isotropic. Thus we are led to assume that the higher terms in this sum are negligible.

For further discussion, we simplify our nomenclature by writing

$$\langle\bar{\epsilon}\rangle \text{ for } \frac{1}{4\pi}\bar{\epsilon}_0^0(T),\; k(T', T) \text{ for } k_0^0(T', T),\; I(T) \text{ for } I_0^0(T) \qquad (10)$$

The resulting form for the cavity integral, omitting all except the lowest term of the sum of eq. (9), is

$$E = \int_0^T dT\, I(T)\bar{S}(T), \qquad (11)$$

where

$$\bar{S}(T) = \int_{T/2}^{T} dT'\,[\langle\bar{\epsilon}(T')\rangle - \langle\bar{\epsilon}(T)\rangle]\,k(T, T') + \int_0^{T/2} dT'\,\langle\bar{\epsilon}(T')\rangle k(T, T') \qquad (11')$$

and no distinction is made in eq. (11') between interactions which are dissipative and those which are not, the second integral includes all interactions, thus expressing the D implicitly. The use of $T/2$ as a limit implies use of free-electron scattering cross sections, and would be changed if more accurate cross sections were used.

The function $\bar{S}$ in eq. (11) differs from the D, which it replaces, in that it incorporates *information about the cavity geometry*. Secondary electrons generated by the fundamental fast electron spectrum are weighted in the second term of eq. (11') by

$$\langle\bar{\epsilon}\rangle = \left(\frac{\langle\bar{\epsilon}\rangle}{T}\right) T$$

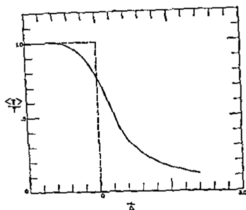


Fig 3 Solid line the fraction of the kinetic energy deposited in a spherical cavity as a function of electron kinetic energy dashed line step function approximation used in computations

where $\langle\bar{\epsilon}\rangle/T$ is the fraction of the secondary electron energy which the secondary leaves in the cavity on the average The first term on the right of eq (11) adjusts the energy deposition by primaries to take account of corresponding energy losses

We have not yet stated assumptions about I and $\langle\bar{\epsilon}\rangle$ which are appropriate for calculations for the I we use the slowing down spectrum for the homogeneous wall case For the $\langle\bar{\epsilon}\rangle$ we use the crude assumption that this equals the electron kinetic energy below a cut off energy Δ, and vanishes above this cut off The value of Δ is chosen according to the size of the cavity, and would be at much higher energies than the other cut off δ, used in determination of D

The calculation of $\bar{S}$ can proceed, with these assumptions It yields exactly the limited stopping power function which ATTIX and I used in our 1955 paper, including the feature of vanishing below Δ

A word needs to be said in justification of the I approximation, and the even more arbitrary $\langle\bar{\epsilon}\rangle$ which have been inserted into eqs (11) and (11) First it should be observed that this choice conserves energy in the homogeneous case if the cross sections used for the calculation of $\bar{S}$ are those also used to determine I Secondly at high energies one expects I to be little affected by the presence of the cavity The main effect of the cavity on the spectrum occurs in a band of kinetic energies for which the electron has a range a little greater or a little less than the diameter of the cavity There would be secondary electrons produced with energies in this band as well as electrons which enter the band from higher energies The component which exhibits the main changes due to the presence of the cavity has moved from higher energies spending part of its

track in both cavity and wall, and has been affected by both albedo differences and differences of track curvature. But this is only part of the spectrum in an energy region which contributes only part of the cavity integral. Thus the assumption that I is the slowing down spectrum for the wall appears to be reasonable, particularly for small cavities and for cavity materials not greatly dissimilar from the wall material.

To discuss the step function approximation to $\langle\bar{\epsilon}\rangle$, let us refer to Fig. 3. The ordinate of this graph gives values for a typical space-averaged energy deposition function for a spherical cavity, as a fraction of the electron kinetic energy (solid curve). — These calculations used straight-ahead and continuous slowing down approximations, as well as the assumption of constant stopping number. They are for non-relativistic electrons in nitrogen. — The dashed curve shows the kind of cut-off approximation used in the 1955 calculations. The abscissa records the electron kinetic energy in units of Δ. One sees here that if Δ is properly chosen, secondary electrons are given a little too much weight below Δ, while they are given too little, i.e. no weight, above Δ.

The discussion to this point has followed from the volume approach. It can be shown that the surface approach leads, for small cavities, to an expression which is formally similar, in that $I(T)$ is multiplied by something like a stopping power and integrated over energy:

$$E = \int_0^T dT\, I(T) \frac{\langle\bar{\epsilon}\rangle_A}{\langle d\rangle_A} \tag{12}$$

where $\langle d\rangle_A$ is an average chord length, and both this function and $\langle\bar{\epsilon}\rangle_A$ are averaged over the inward current of electrons over the whole cavity interface. Because of the formal similarity between eqs. (11) and (12), one can set up an equivalence between the two stopping power-like factors in the two equations, despite differences of definition which follow from the differences of approach. But evaluation of the ratio of averages in eq. (12) has not, to my knowledge, been attempted, except through the indirect route which utilizes eq. (11) and which is subject to the approximations necessary to derive that expression.

Regarding the calculation of energy deposition data for cavities, fairly direct numerical integration procedures were used by SPENCER & ATTIX (1955) and by SPENCER & FANO (1954). BURCH (1955, 1957) has also developed and used a method in which secondary electron production is similarly included, with solution for I otherwise accomplished using continuous slowing down approximation, and with the calculation of I joined operationally to evaluation of the cavity integral so that spectral values need not be recorded.

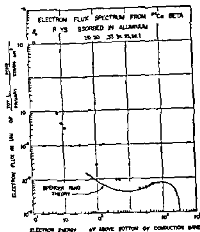


Fig 4 Example of an experimental slowing-down spectrum and comparison with theoretical results using free electron cross section expressions (Courtesy of BIRKHOFF)

Future calculations

Thus far, I have been discussing past calculations Before closing I would like to say a few things about future calculations

We might think of improving the older cavity calculations by using data such as that represented by the solid curve of Fig 3 But it can be proven that results of this kind can be expressed as averages over the more elementary data produced by the cut off approximation Because the existing data varies slowly with Δ, such calculations would amount to little more than a more rational procedure for choosing Δ Even so, such calculations are probably worth doing

More significantly, there exist today the Monte Carlo procedures of BERGER and others which make it possible to break out of the restrictions to small cavities or to cavity materials nearly equivalent to the wall material BURLIN (1966) has called attention to the importance of intermediate and large cavity problems He recommends use of an interpolation between large and small cavity limiting cases From the point of view developed in this lecture, a more fundamental approach would be the evaluation of the source term as well as the surface term in the cavity integral using values for an energy deposition function which are appropriate to the larger cavity sizes One has an option to express such data in the form of multiplicative factors of the type recommended by BURLIN, and this may turn out to be desirable

One aspect of the problem which limits all theoretical results for this class of problems is the knowledge of atomic interactions This can be clearly illustrated as follows In the cavity calculations which were performed in 1955,

as well as others of more recent vintage, the electrons in the medium were treated as subject only to knock on interactions, as described by the Møller cross section with a suitable low energy cut off This is still the dominant approximation, not only in calculations of slowing down spectra but also in the Monte Carlo codes

But in the past ten years or so, there have been produced a body of experimental data on slowing down spectra, due to work by BIRKHOFF and his collaborators (McCONNELL et coll 1965, 1966, 1968) at Oak Ridge National Laboratory Fig 4, which has been reproduced from a recent review paper by BIRKHOFF (personal communication), shows typical results Here the circles represent experimental values, and the solid curves represents a theoretical slowing down spectrum obtained using the simplified cross sections just mentioned The K-shell binding energy comes at about 1 5 keV for aluminum, and at lower energies the two curves diverge by as much as a factor of 4

RITCHIE (McCONNELL et coll 1965), and others, attribute such discrepancies mainly to the omission of Auger electrons produced when vacancies in the K shell are filled, as the atoms readjust after interaction with electrons In addition, however, there are other effects due to inadequacy of the Møller cross section to represent the actual electron scattering cross sections when the primary electron is not far above the binding energy of an atomic shell, or when the secondary electron has little kinetic energy

The point is that effects of this kind have not been included in electron penetration calculations in a general way Discussions of sources of error in existing cavity data have not, to my knowledge, included an analysis of the type or magnitude of error which such effects would produce

I hope that in the near future it will be possible to take some effects of this type into account, both in connection with new tabulations of slowing down spectra and in determination of correspondingly improved cavity data A similar improvement in the Monte Carlo codes should likewise be effected

One last type of calculation deserves mention The older rules and data have proven sufficiently useful and accurate to suggest that the assumptions used in the older studies deserve a quantitative study

SUMMARY

The contributions of GRAY and BRAGG to the theory of energy deposition in cavitie are reviewed in connection with a mathematical formulation of the problem The two principal contributors to the Bragg Gray theory apparently used approaches that were equivalent but dual in the sense of involving adjoint expressions of the energy deposition BURCH has later attempted an extension of Gray s ideas and SPENCER ATTIX have extended the theory by applying Bragg s point of view Some comments on future cavity theory research are included

ZUSAMMENFASSUNG

Es wird eine Übersicht uber die Beitrage von GRAY und BRAGG zur Theorie der Energieabgabe in Kavitaten im Zusammenhang mit einer mathematischen Formulierung des Problems gegeben Die beiden wesentlichen Beitrage zur Bragg Gray Theorie verwendeten offenbar aquivalente Ansatze die jedoch zweifaltig insofern waren als angrenzende Ausdrucke der Energieabgabe beigemischt sind BURCH hat spater eine Erweiterung der Gray schen Ideen versucht und SPENCER ATTIX haben die Theorie durch Anwendung von Braggs Gesichtspunkt erweitert Einige Bemerkungen zur weiteren Forschung der Kavitats Theorie sind eingeschlossen

RÉSUMÉ

L auteur reprend les contributions de GRAY et BRAGG a la théorie du dépot d energie dans les cavites en établissant une formulation mathématique de ce problème Les deux principales contributions à la théorie de Bragg Gray utilisaient apparement des approches qui étaient équivalents mais distinctes dans ce sens qu elles impliquent des expressions voisines du dépot d énergie Plus tard BURCH a essayé d étendre les idées de Gray et SPENCER ATTIX ont étendu cette théorie en appliquant le point de vue de Bragg L auteur ajoute quelques commentaires sur la recherche à venir concernant la théorie des cavités

REFERENCES

BERGER M J Monte Carlo calculation of the penetration and diffusion of fast charged particles *In* Methods in computational physics Vol I Edited by B Alder S Fernbach and M Rotenberg Academic Press New York and London 1953

BIRKHOFF R D Electron flux spectra and radiation yields in solids irradiated by nuclear radiation To be published

BRAGG W H Studies in radioactivity pp 91—99 161—169 MacMillan and Co London 1912

BURCH P R J Cavity ion chamber theory Radiat Res 3 (1955) 361

— Calculations of energy dissipation characteristics in water for various radiations Radiat Res 6 (1957) 289

BURLIN T E A general theory of cavity ionization Brit J Radiol 39 (1966) 727

FANO U Note on the Bragg Gray cavity principle for measuring energy dissipation Radiat Res 1 (1954) 237

GRAY L H The absorption of penetrating radiation Proc roy Soc A122 (1928) 647

— An ionization method for the absolute measurement of γ ray energy Proc roy Soc A156 (1936) 578

LOUTIT J F and SCOTT O C A Louis Harold Gray 1905—1965 Biographical Memoirs of Fellows of the Royal Society 12 (1966) 195

MCCONNELL W J HUBBELL JR H H and BIRKHOFF R D Slowing-down spectrum of ¹⁹ Au beta rays in gold Hlth Phys 12 (1966) 696

— BIRKHOFF R D HAMM R N and RITCHIE R H Electron flux spectra in aluminum analysis for LET spectra and excitation and ionization yields Radiat Res 33 (1968) 216

— HUBBELL JR H H HAMM R N et coll El ctron slowing-down spectrum in Cu of beta rays from ⁶⁴Cu Phys Rev 138 (1965) 1377

MEIXNER J Spezielle Funktionen der mathematischen Physik *In* Handbuch der Physik I, p 197 Springer Verlag Berlin, Heidelberg 1956
O'REILLY B D A variational synthesis method for calculating structure shielding data Report TRC-68 50 (1968) Naval Radiological Defence Laboratory, USA
SELENGUT D S Variational analysis of multi dimensional systems Report HW 59126 (1958) United States Atomic Energy Commission
SPENCER L V and ATTIX F H A theory of cavity ionization Radiat Res 3 (1955) 239
— and FANO U Energy spectrum resulting from electron slowing-down Phys Rev 93 (1954), 1172

FROM THE DEPARTMENTS OF RADIATION PHYSICS (DIRECTOR ASSOC PROF H SKOLDBORN) AND RADIOTHERAPY (DIRECTOR PROF M STRANDQUIST), UNIVERSITY OF GOTHENBURG, SWEDEN

COLLIMATOR AND SCATTERING FOIL FOR 10—20 MeV ELECTRONS

by

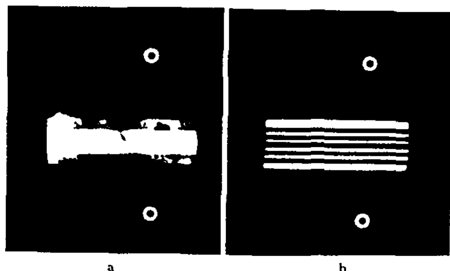
B LINDSKOUG and K A JOHANSSON

This work was initiated by the need for a suitable postoperative technique for treating the internal mammary lymph nodes and was performed on a Brown Boveri Corporation Asklepitron 35 betatron It was assumed that electron radiation in the energy range 10 to 15 MeV would be used and the field size would be 16 cm × 6 5 cm The original collimating system and the scattering foils could not meet the requirements in dose homogeneity *over this* area, excessive scattering and high absorption in the scattering foils made the absorbed dose rate as low 30 rad/min (SSD = 110) at 10 MeV

Scattering foil LOEVINGER et coll (1961) pointed out that a given foil thickness measured in radiation lengths produces equal scattering and bremsstrahlung Materials of high atomic numbers *however*, give rise to somewhat less energy loss

The two original scattering foils consisting of two and three 0 1 mm copper sheets were used in the energy ranges 10 to 25 MeV and 25 to 35 MeV, respectively The copper sheets were soldered together and bonded to a

Submitted for publication 23 March 1970



a b

Fig 1 Roentgenograms of scattering foils a) Original copper foil b) Lead strips

bakelized fabric Fig 1a is a roentgenogram of the thinnest copper foil (The low energy roentgen irradiation will exaggerate the heterogeneity of the foil due to different absorptions in Cu and Sn)

A lead foil, 0 1 mm thick, was initially used in the investigation The scattering was however too marked perpendicular to the plane of acceleration

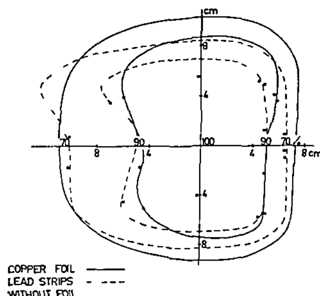


Fig 2 Isodensity lines (70 and 90 %) from film exposures perpendicular to the beam at the maximum depth dose

Table 1

Dose rates (rad/min) at dose maximum in a polystyrene phantom for different foils (SSD = 110 cm)

Energy MeV	Cu 0 2 mm	Au 0 035 mm	Pb strips 0 1 mm	Without foil
10	36	42	49	73
13	62	74	79	116
15	88	105	110	160
20	137	169	178	254

while the dose rate was equal to that of the original copper foil The lead foil was cut into 1 mm strips (Fig 1b) to decrease the scattering Exposures perpendicular to the beam direction were made after removal of all accessories (monitor chamber master collimator and cone) in the electron path the films being placed at the depth of maximum dose The results at 15 MeV with lead strips copper foil and without foil are presented in Fig 2

Variations in the extraction and expansion pulses combined with the oscil lations normally undertaken by the electrons during the acceleration process extend the beam in the acceleration plane The beam flatness was more sym

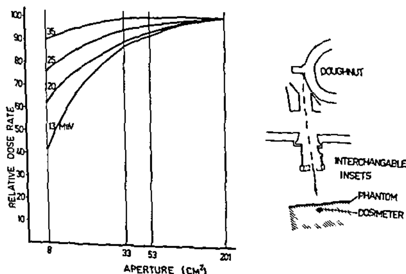


Fig 3 Relative dose rates for different apertures

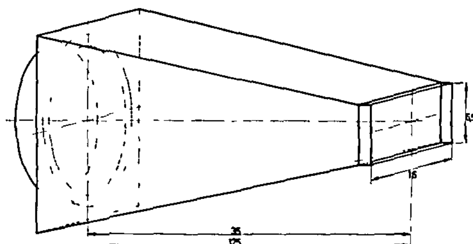


Fig. 4. Schematic drawing of the collimator.

metric with the lead strips than with the copper foil, and the increase in dose rate was about 30 per cent (Table 1).

Measurements were also made with a 0.035 mm gold foil, in order to investigate the properties of a homogeneous foil; this was designed to produce approximately the same mean scattering angle as the lead strips. The symmetry was, however, slightly less than with the lead strips, and the dose rate was about 10 per cent lower (Table 1).

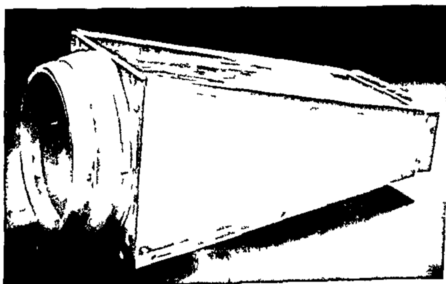


Fig. 5. Final design of the collimator.

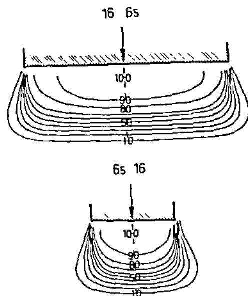


Fig 6 Isodose diagrams for 13 MeV with the new collimator

The lead strips were thus found to possess advantages both in homogeneity and dose rate However at 25 MeV this foil failed to provide enough scattering to comply with the demands of homogeneity

Collimator SVENSSON et coll (1967) have indicated that the dose rate increases markedly with increased aperture (Fig 3)

A collimator, schematically depicted in Fig 4 was designed to function as a funnel allowing as many electrons as possible to pass through the wide opening and scattering them inwards into the treatment region The walls were made of 1 mm brass partly covered by 1 mm lead to afford adequate shielding for energies below 20 MeV The final design is illustrated in Fig 5 The dose

Table 2

Dose rate (rad/min) at dose maximum in a polystyrene phantom with and without brass collimator (SSD = 125 cm)

Energy MeV	With collimator	Without collimator	Increase per cent
10	46	33	40
13	79	57	40
15	113	81	40

rate, measured with and without the collimator walls, increased by 40 per cent with the wall material (Table 2)

The relative surface dose measured with thermoluminescence dosimeters (extruded LiF, Harshaw) was about 92 per cent Isodose diagrams at 13 MeV appear in Fig 6

Conclusion

Although the treatment distance was increased from 110 to 125 cm the dose rate improved with the converging electron collimator in combination with the scattering lead strips The beam flatness was acceptable over an area of 16 cm × 6 5 cm The system is now in routine use

SUMMARY

A new electron collimator design in which scattered electrons increase the dose rate and the flatness of the beam is described The original scattering foil of a BBC Asklepitron 35 betatron has been changed to produce less absorption and thus an improved dose rate

ZUSAMMENFASSUNG

Ein neuartiger Collimator in dem die Streuelektronen die Tiefendose verbessern und eine mehr ebenmässige Dosenverteilung ermöglichen wird beschrieben Die ursprüngliche Streufolie des BBC Asklepitron 35 Betatrons wurde modifiziert um eine verringerte Absorption und eine bessere Strahlenintensität zu erhalten

RÉSUMÉ

Description d un nouveau type de collimateur d electrons grace auquel les electrons dispersés augmentent le débit de dose et donnent une meilleure egalisation du faisceau La plaque de dispersion d origine d un betatron Asklepitron *35 BBC* a ete *modifiee de façon a absorber* moins et à donner ainsi un débit de dose plus élevé

REFERENCES

LOEVINGER R KARZMARK C J and WEISBLUTH M Radiation therapy with high energy electrons Radiology 77 (1961) 906

SVENSSON H and HETTINGER G Influence of collimating systems on dose distribution from 10 to 35 MeV electron radiation Acta radiol Ther Phys Biol 6 (1967) 404

FROM RADIUMHEMMET (DIRECTOR J EINHORN), AND THE DEPARTMENT OF PATHOLOGY (DIRECTOR B THORELL) KAROLINSKA SJUKHUSET STOCKHOLM

RADIOTHERAPY OF INTRACEREBRAL ASTROCYTOMAS

by

B STENBERG and A MOBERG

The treatment of choice of intracranial glioblastoma multiforme (astrocytoma grade 4) is generally considered to be primary surgical decompression and removal of malignant tissue, followed by adequate irradiation (LINDGREN 1969) Radiotherapy of astrocytomas of lesser degrees of malignancy is more controversial BOUCHARD (1966) reported good results with a 5 year survival rate of 49 per cent following surgery and post-operative irradiation in a series of 105 cerebral astrocytomas ZULCH (1963 1969) on the other hand was against radiotherapy of astrocytomas due to the hazards of radiation damage, the risks of increased malignancy and the development of irradiation cancer

The authors as a contribution towards the evaluation of radiotherapy of all grades of astrocytoma have reviewed the records of all patients with brain tumours who received radiotherapy at Radiumhemmet from 1958 to 1966

Material and methods Ninety four patients with brain tumours of all types were treated during the period Forty nine of these (Table 1) fulfilled the requirements for this survey i e they had a tumour of the cerebral hemispheres belonging to the astrocytoma group and had received radiotherapy as described below

Submitted for publication 20 March 1970

rate, measured with and without the collimator walls, increased by 40 per cent with the wall material (Table 2)

The relative surface dose measured with thermoluminescence dosimeters (extruded LiF, Harshaw) was about 92 per cent Isodose diagrams at 13 MeV appear in Fig 6

Conclusion

Although the treatment distance was increased from 110 to 125 cm the dose rate improved with the converging electron collimator in combination with the scattering lead strips The beam flatness was acceptable over an area of 16 cm × 6 5 cm The system is now in routine use

SUMMARY

A new electron collimator design in which scattered electrons increase the dose rate and the flatness of the beam is described The original scattering foil of a BBC Asklepitron 35 betatron has been changed to produce less absorption and thus an improved dose rate

ZUSAMMENFASSUNG

Ein neuartiger Collimator, in dem die Streuelektronen die Tiefendose verbessern und eine mehr ebenmässige Dosenverteilung ermoglichen wird beschrieben Die ursprungliche Streufolie des BBC Asklepitron 35 Betatrons wurde modifiziert um eine verringerte Absorption und eine bessere Strahlenintensitat zu erhalten

RÉSUMÉ

Description d un nouveau type de collimateur d électrons grâce auquel les électrons dispersés augmentent le débit de dose et donnent une meilleure égalisation du faisceau La plaque de dispersion d origine d un betatron Asklepitron 35 BBC a ete modifiée de façon a absorber moins et à donner ainsi un débit de dose plus élevé

REFERENCES

LOEVINGER R KARZMARK C J and WEISSBLUTH M Radiation therapy with high energy electrons Radiology 77 (1961) 906

SVENSSON H and HETTINGER G Influence of collimating systems on dose distribution from 10 to 35 MeV electron radiation Acta radiol Ther Phys Biol 6 (1967) 404

FROM RADIUMHEMMET (DIRECTOR J EINHORN), AND THE DEPARTMENT OF PATHOLOGY (DIRECTOR B THORELL) KAROLINSKA SJUKHUSET, STOCKHOLM

RADIOTHERAPY OF INTRACEREBRAL ASTROCYTOMAS

by

B STENBERG and A MOBERG

The treatment of choice of intracranial glioblastoma multiforme (astrocytoma grade 4) is generally considered to be primary surgical decompression and removal of malignant tissue, followed by adequate irradiation (LINDGREN 1969) Radiotherapy of astrocytomas of lesser degrees of malignancy is more controversial BOUCHARD (1966) reported good results with a 5 year survival rate of 49 per cent following surgery and post-operative irradiation in a series of 105 cerebral astrocytomas ZULCH (1963 1969) on the other hand, was against radiotherapy of astrocytomas due to the hazards of radiation damage the risks of increased malignancy and the development of irradiation cancer

The authors as a contribution towards the evaluation of radiotherapy of all grades of astrocytoma have reviewed the records of all patients with brain tumours who received radiotherapy at Radiumhemmet from 1958 to 1966

Material and methods Ninety four patients with brain tumours of all types were treated during the period Forty nine of these (Table 1) fulfilled the requirements for this survey i e they had a tumour of the cerebral hemispheres belonging to the astrocytoma group and had received radiotherapy as described below

Submitted for publication 20 March 1970

Table 1

Age and sex distribution in patients with astrocytoma

Astrocytoma	Sex		Total number of patients	Average age and range in years
	Male	Female		
Grade 1	9	5	14	34 (7—67)
Grade 2	6	6	12	44 (12—73)
Grade 3	7	3	10	47 (31—62)
Grade 4 (glioblastoma multiforme)	10	3	13	50 (14—67)
Total	32	17	49	43 (7—73)

Therapy Subtotal resection was performed in 45 patients and 4 patients were primarily considered to be inoperable Forty seven patients were treated with a kilocurie cobalt unit and two with betatron The patients were assessed individually and treatment was given over two fields with a 90° angle between the radiation beams and wedge filters The sizes of the irradiation fields were determined from the surgical and radiologic findings so as they covered the tumour by a definite margin At that time an entire hemisphere or the whole brain was never exposed to irradiation The doses ranged from 3 000 to 6 800 rad over 6 to 8 weeks

Pathology All the available material from the biopsy specimens and autopsies was re examined Tumours belonging to the astrocytoma group — after exclusion of subjects with insufficient tumour material and growths of other types (including malignant oligodendrogliomas) — were classified according to the system of KERNOHAN & SAYRE (1952), i e grade 1 corresponded to fibrillary or protoplasmic astrocytoma and grade 4 to glioblastoma multiforme

Grading tumours is an exercise in controlled capriciousness When there was doubt between grades 1 and 2 or between 2 and 3, the tumour was referred to the greater degree of malignancy The criteria for a diagnosis of glioblastoma multiforme were, in addition to the malignant cell population, the presence of 'glomerular abnormal blood vessels and necroses with pallisaded tumour cells

Autopsy material was available from 15 subjects The microscopic appearances of the autopsy material were compared with those of the previous biopsy specimens with particular regard to irradiation effects, i e fibrinoid necrosis of vessels walls and perivascular paramyloid deposits (ZULCH 1960)

Table 2

Survival periods after completed irradiation in patients with astrocytoma

Astrocytoma	Total number of patients	Number of survivors and periods (in months)						
		0—1	6	12	18	24	36	48
Grade 1	14	12	10	9	6	5	5	4*
Grade 2	12	11	9	6	4	4	3	2**
Grade 3	10	10	7	6	2	2	1	0
Grade 4 (glioblastoma multiforme)	13	12	7	4	1	0	0	0
Total	49	45	33	25	13	11	9	6

* Two with epileptiform episodes two clinically healthy

** Both with epileptiform episodes of the Jacksonian type one hemiparetic

Results

The number of patients in each tumour group and their survival periods are listed in Table 2 nine of 49 patients survived for 3 years and six for 4 years

Signs of irradiation effects could be identified in brain tissue from eight of the 15 patients examined at autopsy All eight patients had the vascular stigmas of irradiation within the malignant tissue Five of these patients representing all those from whom macroscopically normal brain tissue had been taken at autopsy also had obvious evidence of irradiation effects (fibrinoid necrosis of vessel walls and perivascular para amyloid deposits) outside the tumour The average irradiation dose for these five patients was 5 000 rad (4 000 to 6 800) and the average duration of treatment was 35 days (27 to 48)

Discussion

The fate of the patients of the present material with astrocytoma grade 4 (glioblastoma multiforme) (4 out of 13 survived one year but none two years) fits in with the results published by SACHS (1954) and FRANKEL & GERMAN (1958) i e a one year survival rate of about 15 per cent BOUCHARD (1966) however reported better survival rates 44 per cent at one year, 13 per cent at 3 years and a 7 per cent rate at 5 years

Eight (or 31 per cent) of the 26 patients with astrocytoma grades 1 and 2 survived for more than three years After surgical treatment alone, MACCARTY (1962) reported a 3 year survival rate of 64 per cent (14 of 22 patients) LEVY & ELVIDGE (1956) and BOUCHARD (1966) had practically the same 3 year survival

Table 1

Age and sex distribution in patients with astrocytoma

Astrocytoma	Sex		Total number of patients	Average age and range in years
	Male	Female		
Grade 1	9	5	14	34 (7—67)
Grade 2	6	6	12	44 (12—73)
Grade 3	7	3	10	47 (31—62)
Grade 4 (glioblastoma multiforme)	10	3	13	50 (14—67)
Total	32	17	49	43 (7—73)

Therapy Subtotal resection was performed in 45 patients and 4 patients were primarily considered to be inoperable Forty seven patients were treated with a *kilocurie cobalt unit* and two *with betatron* The patients were assessed individually and treatment was given over two fields with a 90° angle between the radiation beams and wedge filters The sizes of the irradiation fields were determined from the surgical and radiologic findings so as they covered the tumour by a definite margin At that time an entire hemisphere or the whole brain was never exposed to irradiation The doses ranged from 3 000 to 6 800 rad over 6 to 8 weeks

Pathology All the available material from the biopsy specimens and autopsies was re examined Tumours belonging to the astrocytoma group — after exclusion of subjects with insufficient tumour material and growths of other types (including malignant oligodendrogliomas) — were classified according to the system of KERNOHAN & SAYRE (1952), i e grade 1 corresponded to fibrillary or protoplasmic astrocytoma and grade 4 to glioblastoma multiforme

Grading tumours is an exercise in controlled capriciousness When there was doubt between grades 1 and 2 or between 2 and 3, the tumour was referred to the greater degree of malignancy The criteria for a diagnosis of glioblastoma multiforme were, in addition to the malignant cell population, the presence of glomerular' abnormal blood vessels and necroses with pallisaded tumour cells

Autopsy material was available from 15 subjects The microscopic appearances of the autopsy material were compared with those of the previous biopsy specimens with particular regard to irradiation effects, i e fibrinoid necrosis of vessels walls and perivascular paramyloid deposits (ZULCH 1960)

SUMMARY

The survival rate of 49 patients with intracerebral astrocytoma of all grades of malignancy was reviewed It became apparent that a comparison and assessment of different therapeutic measures requires knowledge of the neurologic state of the patient following surgery and before and after radiotherapy The potential hazards of radiation effects on brain tissue outside the tumour must be duly considered when planning the latter

ZUSAMMENFASSUNG

Die Überlebungsraten von 49 Fallen von Astrocytoma verschiedener Schweregrade wurde statistisch erfasst Es zeigte sich dass es notwendig ist den neurologischen Status des Pa tienten vor wahrend und nach der therapeutischen Bestrahlung genau zu kennen bevor man die Wirksamkeit der Bestrahlung vergleichend einschatzen kann Vor der Behandlung ist es notwendig einen Plan aufzustellen der auch die Gefahren der Bestrahlung auf die umgebenden Gehirnzellen berucksichtigt.

RÉSUMÉ

Les auteurs ont passe en revue le taux de survie de 49 malades atteints d astrocytome in tracerebral de tous grades de malignite Il est apparu que la comparaison et l apprecia tion des differentes mesures therapeutiques necessitent la connaissance de l etat neurologi que du malade après l intervention chirurgicale et avant et apres la radiothérapie Pour etablir le plan du traitement par les radiations il faut tenir compte des risques qu il peut comporter pour le tissu cerébral situe en dehors de la tumeur

REFERENCES

BERG N O and LINDGREN M Time-dose relationship and morphology of delayed radiation lesions of the brain in rabbits Acta radiol (1958) Suppl No 167

BOUCHARD J Radiation therapy of tumours and disease of the nervous system Lea & Febiger Philadelphia 1966

FRANKEL S A and GERMAN W J Glioblastoma multiforme Review of 219 cases with regard to natural history pathology diagnostic methods and treatment J Neurosurg 15 (1958) 489

KERNOHAN J W and SAYRE G P Tumours of the central nervous system Armed Forces Institute of Pathology Washington 1952

KRAMER S Tumour extent as a determining factor in radiotherapy of glioblastomas Acta radiol Ther Phys Biol 8 (1969) 111

LEGRE J AMALRIC R et Padaut J L irradiation des glioblastomes multiformes Acta radiol Ther Phys Biol 8 (1969) 118

LEVY L F and ELVIDGE A R Astrocytoma of the brain and spinal cord a review of 176 cases 1940—1949 J Neurosurg 13 (1956) 413

LINDGREN M Discussion to Round Table Conference 8th Symposium Neuroradiologicum Paris 1967 Acta radiol Ther Phys Biol 8 (1969) 182

MACCARTY C S Results of the surgical management of glial tumours of the brain *In* The biology and treatment of intracranial trumous p 434 Edited by W S Fields and P C Sharkey Charles C. Thomas Springfield Illinois 1962

rate after combined surgical and radiologic therapy but they considered the 5 year prognosis to be better with combined therapy

The present therapy results with astrocytoma grades 1 and 2 seem to be less promising than those reported from USA and Canada There are, however, factors other than crude survival rates to be taken into account One of these is the sizes of the irradiation fields which, in this series, were limited Another factor is dosage, the patients received between 4 000 and 5 000 rad, somewhat less than the 5 000 to 6 000 rad used by BOUCHARD (1966) and the 5 000 to 7 000 rad of LEGRE et coll (1969)

A second and probably more important factor in explaining the divergent results is the selection of patients Practically all intracranial tumours diagnosed in Sweden are operated upon and a limited number are also given radiotherapy This represents a selection of patients, probably a negative selection, with a predominance of those in poor condition being referred to radiotherapy Two of the 14 patients with astrocytoma grade 1 died within a month following radiotherapy This appears to be evidence that the condition of patients making up the series was poor Comparison of different therapeutic measures is, in fact, unfruitful without knowledge of the neurologic state of the patients following surgery but before and after radiotherapy To take this into account when making a retrospective survey is often impossible as has been apparent in the present series

Morphologic signs of irradiation effects (fibrinoid necrosis of vessel walls and perivascular para amyloid deposits) outside the tumour were demonstrated in the brains of 5 patients It is quite conceivable that the true incidence might have been much higher than would appear from the post mortem material available, the specimens were collected at different hospitals where the major interest was focussed solely upon the growth

The irradiation doses used were somewhat lower than those recommended internationally although within the therapeutic limits of BERG & LINDGREN (1958) Since there are no grounds for assuming that morphologic detectable irradiation effects can be directly related to specific clinical signs in patients with brain tumours it appears to have become important to determine with much greater precision the risk and significance of side effects of early and late irradiation damage on brain tissue outside the tumour This consideration assumes even greater proportions in the face of proposals to irradiate the entire involved hemisphere (LEGRE et coll 1969) or the whole brain (KRAMER 1969) in treating astrocytoma grade 4 (glioblastoma multiforme)

The survey was originally intended as an assessment of radiotherapy of intra cerebral astrocytoma in adults It has however posed more questions than it has answered and has indicated the need for a prospective study with radio therapists neurologists and pathologists working as a team

SUMMARY

The survival rate of 49 patients with intracerebral astrocytoma of all grades of malignancy was reviewed. It became apparent that a comparison and assessment of different therapeutic measures requires knowledge of the neurologic state of the patient following surgery and before and after radiotherapy. The potential hazards of radiation effects on brain tissue outside the tumour must be duly considered when planning the latter.

ZUSAMMENFASSUNG

Die Überlebensraten von 49 Fällen von Astrocytoma verschiedener Schweregrade wurde statistisch erfaßt. Es zeigte sich, dass es notwendig ist, den neurologischen Status des Patienten vor, während und nach der therapeutischen Bestrahlung genau zu kennen, bevor man die Wirksamkeit der Bestrahlung vergleichend einschätzen kann. Vor der Behandlung ist es notwendig einen Plan aufzustellen, der auch die Gefahren der Bestrahlung auf die umgebenden Gehirnzellen berücksichtigt.

RÉSUMÉ

Les auteurs ont passé en revue le taux de survie de 49 malades atteints d'astrocytome intracérébral de tous grades de malignité. Il est apparu que la comparaison et l'appréciation des différentes mesures thérapeutiques nécessitent la connaissance de l'état neurologique du malade après l'intervention chirurgicale et avant et après la radiothérapie. Pour établir le plan du traitement par les radiations, il faut tenir compte des risques qu'il peut comporter pour le tissu cérébral situé en dehors de la tumeur.

REFERENCES

BERG N. O. and LINDGREN M.: Time-dose relationship and morphology of delayed radiation lesions of the brain in rabbits. Acta radiol. (1958) Suppl. No. 167.

BOUCHARD J.: Radiation therapy of tumours and disease of the nervous system. Lea & Febiger, Philadelphia 1966.

FRANKEL S. A. and GERMAN W. J.: Glioblastoma multiforme. Review of 219 cases with regard to natural history, pathology, diagnostic methods and treatment. J. Neurosurg. 15 (1958), 489.

KERNOHAN J. W. and SAYRE G. P.: Tumours of the central nervous system. Armed Forces Institute of Pathology, Washington 1952.

KRAMER S.: Tumour extent as a determining factor in radiotherapy of glioblastomas. Acta radiol. Ther. Phys. Biol. 8 (1969), 111.

LEGRÉ J., AMALRIC R. et PALAUT J.: L'irradiation des glioblastomes multiformes. Acta radiol. Ther. Phys. Biol. 8 (1969), 118.

LEVY L. F. and ELVIDGE A. R.: Astrocytoma of the brain and spinal cord: a review of 176 cases 1940—1949. J. Neurosurg. 13 (1956), 413.

LINDGREN M.: Discussion to Round Table Conference. 8th Symposium Neuroradiologicum, Paris 1967. Acta radiol. Ther. Phys. Biol. 8 (1969), 182.

MACCARTY C. S.: Results of the surgical management of glial tumours of the brain. *In*: The biology and treatment of intracranial tumours, p. 431. Edited by W. S. Fields and P. C. Sharkey. Charles C. Thomas, Springfield, Illinois 1962.

SACHS E The treatment of glioblastomas with radium J Neurosurg 11 (1954), 119
ZÜLCH K J Über die Strahlensensibilität der Hirngeschwulste und die sogenannte Strahlen Spätnekrose des Hirns IX Internat Congress of Radiology, München 1959 Georg Thieme Verlag Stuttgart 1960
— Morphologische Veranderungen an Geschwulsten nach Bestrahlung und Schadigungs möglichkeiten am normalen Hirn Strahlenforschung und Strahlenbehandlung 4 (1963), 47
— Roentgen sensitivity of cerebral tumours and so-called late irradiation necrosis of the brain. Acta radiol Ther Phys Biol 8 (1969), 92

FROM THE DEPARTMENTS OF RADIATION PHYSICS (DIRECTOR PROF K. LIDÉN) AND RADIOTHERAPY (DIRECTOR PROF M LINDGREN), THE UNIVERSITY HOSPITAL, LUND, SWEDEN

MANTLE TREATMENT OF HODGKIN'S DISEASE WITH COBALT 60

Technique and dosimetry

by

GUDRUN SVAHN TAPPER and TORSTEN LANDBERG

Radiotherapy has been the method of choice in the treatment of clinically local lesions since PUSEY (1902) described the effects of the irradiation of Hodgkin's disease. It has long been assumed that Hodgkin's disease is always progressive and fatal (PATERSON & PATERSON 1954) and that it is not possible to predict the site of late manifestations (NICE & STENSTROM 1954). Irradiation has therefore been confined to clinically involved regions. In recent years however it has been questioned whether the disease is systemic or whether it may not sometimes be initially local and thus curable (CRAVER 1954, KAPLAN 1962 and 1966, EASSON & RUSSEL 1963, PETERS 1966 and MUSSHOFF & BOUTIS 1967). Experience has also suggested that the first progression often occurs in lymph node groups adjacent to those initially involved (JELLIFFE 1965, NEWALL 1965, KAPLAN 1966, ROSENBERG & KAPLAN 1966, LANDBERG & LARSSON 1968 and LANDBERG 1969). In contrast with SCHEER (1963), MUSSHOFF & BOUTIS (1967) and KAPLAN (1968) claimed that the prognosis tends to vary with the completeness of the first remission.

Submitted for publication 26 January 1970

Sachs E The treatment of glioblastomas with radium J Neurosurg 11 (1954), 119
Zülch K J Über die Strahlensensibilität der Hirngeschwulste und die sogenannte Strahlen Spatnekrose des Hirns IX Internat Congress of Radiology, Munchen 1959 Georg Thieme Verlag Stuttgart 1960
— Morphologische Veranderungen an Geschwulsten nach Bestrahlung und Schadigungs möglichkeiten am normalen Hirn Strahlenforschung und Strahlenbehandlung 4 (1963) 47
— Roentgen sensitivity of cerebral tumours and so-called late irradiation necrosis of the brain Acta radiol Ther Phys Biol 8 (1969), 92

LAN & ROSENBERG (1966) recommended such irradiation but FULLER et coll (1967) only when clinically indicated If mediastinal or hilar involvement is massive PETERS (1966) KAPLAN (1966) and KAPLAN & ROSENBERG (1966) include the lungs in the fields during part of the treatment and in the course of treatment the thoracic parts of the fields are narrowed SALZMAN et coll (1964) JELLIFFE (1965) and KAPLAN & ROSENBERG (1966) used a spinal shield in the dorsal field during part of the treatment SALZMAN et coll (1964) utilized the diaphragm as the caudal border of the target JELLIFFE (1965) the second lumbar vertebra while RUBIN & KUROHARA (1966) employed a level below the diaphragm

KAPLAN (1962 and 1966) used a 6 MV linear accelerator, SALZMAN *et coll* (1964) a 2 MeV Van de Graaff generator, while PETERS (1966) STRICKSTROCK et coll (1967) and FULLER et coll (1967) employed cobalt units

From an investigation of the literature on the variation of the recurrence rate with dose KAPLAN (1966) suggested that a dose of approximately 4 000 rad, given at the rate of approximately 1 000 rad/week is a reasonable estimate of the tumoricidal dose in Hodgkin's disease Similar absorbed dose levels have been reported by KAPLAN (1962) and KAPLAN & ROSENBERG (1966) (3 500—4 000 rad tumour dose in three to four weeks), JELLIFFE (1965) (3 000 rad in 3 weeks) PETERS (1966) (± 3 500 rad in 3 weeks) RUBIN & KUROHARA (1966) ('depth dose ranging from a minimum of 4 000 R to a maximum of 5 000 R) FULLER (1967) and FULLER et coll (1967) (tumour dose 4 000 rad in 4 weeks), MUSSHOFF & BOUTIS (1968) (focal dose of 4 000 R in affected areas and 3 500 R in the adjacent unaffected regions) and NOBLER (1968) (tumour dose 3 000 rad in 2 weeks or 3 500 rad in 3 to 4 weeks) SALZMAN et coll (1964) recommended 2 400 R measured at the midplane/3 weeks up to 3 000 or 3 500 R *If there is a residual mass* SALZMAN et coll (1964) JELLIFFE (1965) and FULLER (1967) give additional treatment PETERS (1966) RUBIN & KUROHARA (1966) *and* FULLER *(1967)* like MUSSHOFF & BOUTIS (1968) give smaller doses to the clinically uninvolved lymph node groups

FULLER et coll (1967) gave a smaller absorbed dose to the dorsal field (two thirds of the dose delivered *to* the ventral field) and calculated the absorbed dose distribution by the CLARKSON *(1941) method* The absorbed dose was reported as the tumour dose delivered to the mid mediastinum RUBIN & KUROHARA (1966) reported the use of a bolus to fill the space over the shoulders and both sides of the neck Generally the reports *contain little* information about dosimetry for the individual patient and often do not state whether the absorbed doses reported have been *corrected for tissue* inhomogeneity

ANDERSON et coll (1969) in a phantom study found that elimination of the neck and supraclavicular regions from *the portals* for 20 per cent of the time

In view of the above conclusions, patients with clinically local lesions (stages I or II according to JELLIFFE & THOMSON 1955, JELLIFFE 1965 and ROSENBERG 1966) are now often treated with irradiation not only of the clinically involved lymph node groups but also of those adjacent and apparently uninvolved. Results of such treatment have been reported by GILBERT (1928), PETERS (1950 and 1966), PETERS & MIDDLEMISS (1958), KAPLAN (1962 and 1968), SALZMAN et coll. (1964), JELLIFFE (1965), KAPLAN & ROSENBERG (1966), RUBIN & KUROHARA (1966), STRICKSTROCK et coll. (1967), MUSSHOFF & BOUTIS (1968) and SMITHERS (1969).

In most cases of stage I or stage II the disease is *limited to one or more of the* lymph node groups in the neck, in the supra-infraclavicular region, axilla or mediastinum (WESTLING 1965, KAPLAN 1966, LANDBERG & LARSSON 1968 and 1969, and LANDBERG 1969). Most authors in the treatment of such cases have used the method described by KAPLAN (1962), i.e. a megavoltage mantle technique with ventral and dorsal opposed fields and lead blocks interposed to protect presumably healthy tissues.

Certain technical modifications of the mantle technique have been reported. Thus, while KAPLAN (1962 and 1966), SALZMAN et coll. (1964), JELLIFFE (1965) and KAPLAN & ROSENBERG (1966) used a dorsal field similar to the ventral field, PETERS (1966), RUBIN & KUROHARA (1966), FULLER (1967) and FULLER et coll. (1967) employed dorsal fields only for the more deep seated parts of the volume to be irradiated. STRICKSTROCK et coll. (1967) used several ventral and dorsal fields, tilted so as to avoid under- or overdosage in the inter-fields. The patients of SALZMAN et coll. (1964) sat during treatment, while those of RUBIN & KUROHARA (1966) reclined. KAPLAN (1962), SALZMAN et coll. (1964), RUBIN & KUROHARA (1966) and NOBLER (1968) stressed the importance of irradiating the lymph nodes in the neck up to the tip of the mastoid. To avoid irradiation of the eyes, the patients' heads were extended during treatment in the series reported by SALZMAN et coll. (1964), JELLIFFE (1965), RUBIN & KUROHARA (1966), FULLER (1967), FULLER et coll. (1967) and STRICKSTROCK et coll. (1967). A large dose to the cerebellum then seems unavoidable, the lower teeth also receive considerable irradiation (SALZMAN et coll. 1964). There seems to be general agreement that the vocal cords can be safely protected in the ventral field, a shield being carried up to the cranial border of the field by RUBIN & KUROHARA (1966), FULLER (1967) and FULLER et coll. (1967), thus leaving submental nodes unirradiated from the ventral field. If the infraclavicular lymph nodes are to be irradiated, the cranial parts of the lungs must receive a large dose down to the level of the fourth rib posteriorly (JELLIFFE 1965). Opinions differ as to whether the pulmonary hila should be irradiated in the absence of demonstrable hilar involvement. KAPLAN (1962 and 1966) and KAP-

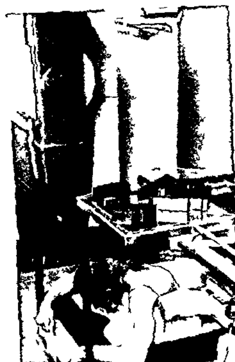


Fig 2 Arrangement for irradiation treatment in prone position

nodes to the supra and infraclavicular fossae to the axillae and to the me *diastinum* including the pulmonary hila The caudal border of the target was set at Th12 Treatment was given with cobalt 60 to one ventral and one dorsal field in both supine and prone positions The build up effect of the cobalt 60 radiation was thus retained and the risk of skin reactions was minimized

Equipment A cobalt 60 unit (Siemens Gammatron III diameter of source ≈ 1 5 cm) was used The primary collimator was a block diaphragm of tungsten with its distal edges 23 8 cm from the source The cobalt unit was equipped with a light beam that indicated the 50 % isodose line at a depth of 0 5 cm in a 10 cm × 10 cm field In order to make the field large enough (about 40 cm × 40 cm) the SSD had to be at least 130 cm and the patients had to lie on a low couch The lead absorbers were placed on a 0 8 cm perspex plate at a distance of 107 cm from the cobalt source (Fig 2) The absorbers were 5 cm thick with vertical sides

Posture during treatment To diminish the alteration in patient contour on change of posture from supine to prone and to facilitate the treatment ar

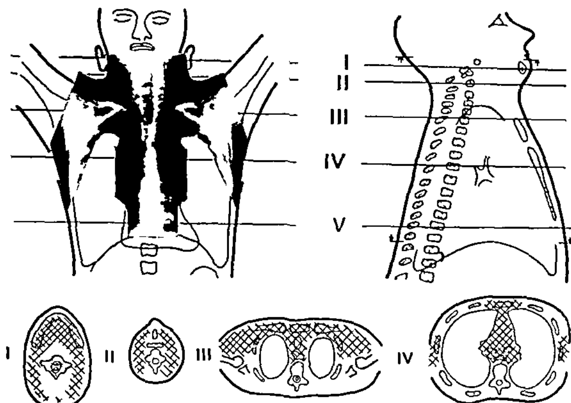


Fig 1 Schematic drawing of a ventral field one sagittal and four (I—II—III—IV) transversal sections The target regions are indicated by the cross hatched parts

gave a range of the absorbed dose in the particular example studied of about ± 10 per cent of the reference value

A dosimetric study in an Alderson phantom using a ^{60}Co unit was reported by MEURK et coll (1968) Measurements indicated the absorbed dose to the pelvic structures such as the ovaries to be approximately 65 rad for 4 000 rad to the mid mediastinum

The purpose of the present report was to demonstrate planning and follow up of the absorbed dose delivered by mantle treatment with cobalt 60 to patients with Hodgkin's disease

Methods

Treatment An absorbed dose of 4 000 rad in 9 weeks (split course) with 24 fractions was to be delivered to the lymph node groups (Fig 1) on both sides of the neck up to the tip of the mastoid, including the submental and submandibular

field No absorbers were used to shield the spinal cord or the oral cavity No bolus was used

A beam flattening filter (filter A SVAHN TAPPER 1970) and an individual contour compensating filter made of copper were sometimes used The source filter distance was 30 2 cm The filters compensated only for the craniocaudal direction The caudal edge of the field with the beam flattening filter was not 3 but 2 cm lower than that of the projected target

Dose planning and dose measurements The word dose signifies absorbed dose in the present investigation Dose planning was always done in the sagittal section and in 10 patients in the cross sections as well The isodose charts and depth dose data used have been described by SVAHN TAPPER (1970) The isodose shift method (DUTREIX & DUTREIX 1962) was employed for correction of the angle of incidence For practical reasons the isodoses were shifted parallel to the central beam everywhere except in the axillary region, where the isodoses were shifted in the direction of the local beam since the two methods give very different results in this region with tangential irradiation and because the isodoses had been shifted parallel to the local beam in the phantom studies Dose planning was first done for the sagittal section and the depth doses thus obtained at different levels were then used when dose planning the transversal sections

Doses delivered during treatment were measured with small (0 5 cm × 2 cm air volume 0 3 cm³) condenser chambers Single chambers were placed in the auditory canal and adjacent to the eyes Plastic catheters containing 6 to 18 chambers were laid along different lines on the front and back of the patient and passed twice to three times down into the hypopharynx and the oesophagus The catheters placed on the skin were fastened in position The absorbed dose determined represented the absorbed dose at the measurement point for complete treatment The catheters used on the skin were thick enough to allow full electron equilibrium their positions were checked with slow films exposed during treatment Fig 3a) and with roentgen films of known magnification (Fig 9)

The dose plans and the dose measurements made inside and on the patients were the basis for the individual dose calculations

Both fields received the same peak absorbed dose in the central beam All figures in the isodose charts are written on the higher dose side of the isodose lines The AP distance denotes the length of the line between the ventral and the dorsal surface at any level of the sagittal section in the symmetric plane The central point on the AP line is called AP/2 or 0 (see Figs 7, 8 11 and 13 and the Table) When an absorbed dose is compared with the AP/2 dose the comparison is made with the AP/2 dose at the same level (i e in the same cross section)



Fig 3 a) Slow film of a ventral field exposed during treatment The positions of the plastic catheters containing condenser chambers are seen but not the borders of the field b) Slow film showing the cranial parts of a ventral field (The transversal column at the level of the shield for the vocal cords represents part of the wooden support for the plastic shell)

rangement, it was necessary to produce plastic shells These shells were made to measure, a ventral one for the prone position and a dorsal shell for the supine position, from a positive plaster cast of the patient with the neck in hyperextension and the hands above the head The correct treatment position of the patient was also checked with large cardboard sheets in which the sagittal contours had been cut out Roentgen films of known magnification of barium in the oesophagus were taken in the two treatment positions Five vertical sections of the patients were drawn (Fig 1), viz cross sections at the level of the chin and auditory canal (= cranial border of the target), vocal cords, jugulum and pulmonary hila, together with a sagittal section in the symmetric plane

Definition of treatment fields The borders of the target were projected up *vertically to the skin of the patient in each of the treatment positions* The edges of the field exceeded the projected target by 3 cm Lead absorbers were used to *produce an irregular field with its edges lying 1 cm outside the target area* marked on the patient's skin The broad penumbra was however left un*diminished along the caudal border to facilitate the addition of abdominal fields* Roentgen films exposed in the two treatment positions and slow films exposed *during treatment (Fig 3) were used to decide the definite positions of the ab*sorbers Slow films were also exposed frequently during the entire treatment *period to check the reproducibility of the arrangement The positions of the lead* absorbers were marked on a cellophane film placed on the perspex plate, and to *facilitate initiation of the second series some reference points* were tattooed on the patient's skin The field borders were also marked on the skin of the patient *The two fields were similar* except for shielding of the vocal cords in the ventral

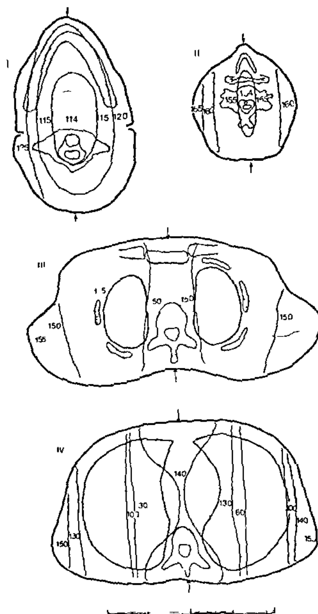


Fig 5 Dose distribution in the four transversal sections (I—II—III—IV of fig 1) of the same patient as in fig 4 No beam flattening filter was used and no correction was made for the presence of lung tissue in the hilar regions

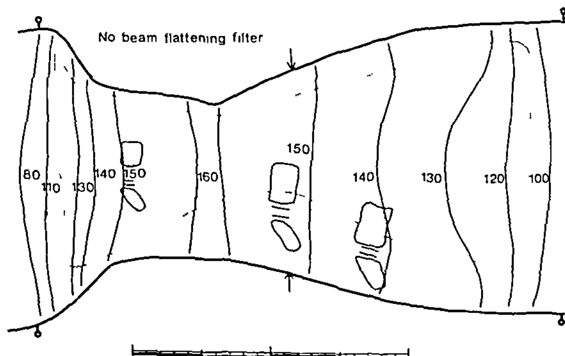


Fig 4 Dose distribution in the sagittal section of a patient No beam flattening filter was used The dotted contour indicates the target

Results and Discussion

Dose distribution in a patient The dose distribution in the sagittal section in the symmetric plane of a patient is shown in Fig 4 No beam flattening filters were used The absorbed dose varied from 115 % at the cranial and caudal borders of the target to 160 % in the neck The dose distribution in the four transversal sections (I—II—III—IV, Fig 1) for the same patient as in Fig 4 is given in Fig 5 In section I, the absorbed dose varied from 115 % to 125 %, in section II from 155 % to 165 %, in section III from 145 % at the top of the axilla to 150 % centrally and laterally in the axilla, and in section IV, where the absorbed dose was not corrected for the presence of lung tissue in the hilar regions, it varied from 130 % to 150 % In sections I and II, the AP/2 dose corresponded to the minimum absorbed dose in the sections, and the maximum doses were 5 % to 10 % higher In sections III and IV, the AP/2 dose corresponded to the maximum absorbed doses in the sections, and the minimum absorbed doses were about 7 % smaller at the top of the axilla The dose distribution in this patient was representative

The wide variation in the target absorbed dose in craniocaudal direction requires successive reduction of the field according to the individual dose distribution or the use of a beam flattening filter Fig 6 (upper diagram) gives the do e distribution in the sagittal section with such a filter for the same case as illustrated in Fig 4 The variation in absorbed dose in the target is reduced to between 135 % and 160 % When an individual filter compensating for the neck contour was al o u ed the variation was reduced further (Fig 6) (lower diagram) to between 135 % and 150 % where the maximum absorbed dose in the sagittal section was situated at the level at which the absorbed dose in the corresponding cross section (III) had its minimum more laterally i e at the level of the top of the axilla (cf Fig 5)

Absorbed dose at point AP/2 at five different levels as function of different a p distances Do e plans were made in the sagittal section and in four transversal sections (I—II—III—IV Fig 1) for the first ten patients receiving mantle treatment

No beam flattening filters were used but towards the end of the treatment period the variation of the total absorbed dose in the target was diminished by successive reduction of the fields The dose distribution in these ten patients form the basis of the curves in Fig 7 The diagram shows the planned dose at point AP/2 as a function of different anteroposterior distances at five levels (sections I—II—III—IV Fig 1 and the level of Th12 i e 3 cm cranial to the field border) The patients five men and five women differed considerably in body build The individual points in the diagram differ by less than ± 5 % of the AP/2 dose from the curves in Fig 7 Fig 8 gives the corresponding diagram for beam flattening filter A both in the ventral and the dorsal fields and is based on dose plans for 18 patients (SVAHN TAPPER 1970) The individual points in the diagram differ by less than ± 5 % of the AP/2 dose from the curves in Fig 8

When the a p distance in the centre of the field was very small compared with that at the cranial and caudal borders of the target filter B (SVAHN TAPPER 1970) was used in the ventral field combined with filter A in the dorsal field The number of these patients was not large enough to warrant a diagram for such a combination

Comparison between planned and measured absorbed dose in the sagittal section It is always desirable to control the absorbed dose as near the target as possible The hypopharynx and the oesophagus are appropriate places for such measurements since these are situated centrally in the target Besides measurements made there represent the absorbed dose near the centre of the patient and include the effect of a possible shift in position of the viscera between the two treatment postures Fig 9 represents chest roentgenograms of known magnifica

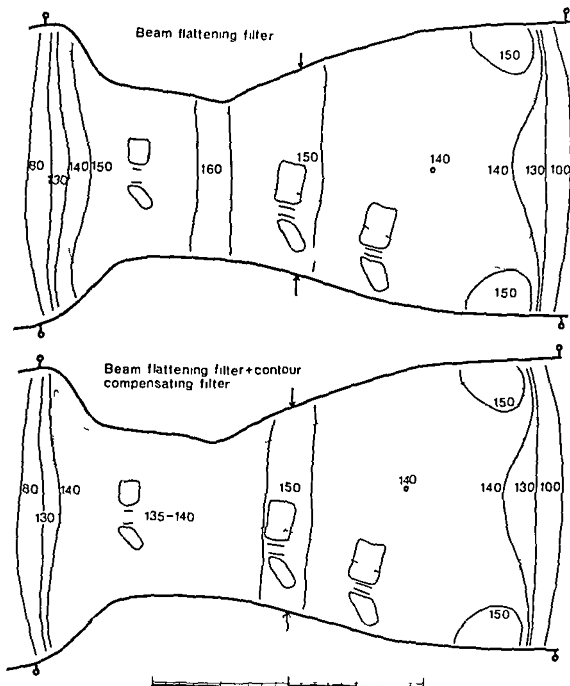


Fig. 6. Dose distribution in the sagittal section of the same patient as in figs 4 and 5. *Top*

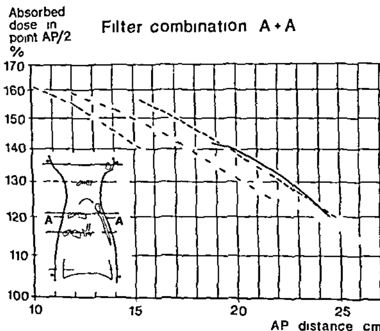


Fig 8 Absorbed dose in the sagittal section at point AP/2 at the levels of five transversal sections (I—II—III—IV fig 1 and at the level of Th12) as function of different a.p distances in the sections Beam flattening filter was used Both fields received the same peak absorbed dose = 100 %

sorbed doses measured with condenser chambers in the hypopharynx and in the oesophagus are denoted by crosses in Fig 10 The crosses represent the mean value of two measurements during two treatments When one chamber was discharged the corresponding cross in Fig 10 denotes only one measurement If more than one third of the chambers in a catheter were discharged another measurement was made in the patient

The patients in Fig 10 were chosen to represent a range of various anteroposterior distances The position of the catheters in relation to the trachea was determined by slow films exposed during treatment and, to facilitate a comparison with the planned dose the measured values in Fig 10 were corrected for the presence of gas in the trachea According to phantom studies (SVAHN TAPPER 1970) this correction is — 7 % of the peak absorbed dose in the ventral field In the planned dose (solid and broken lines Fig 10) there is a variation of ± (1—2) % in the peak absorbed dose due to the area of the field Further, the sagittal sections of the patients are only approximate since they were drawn

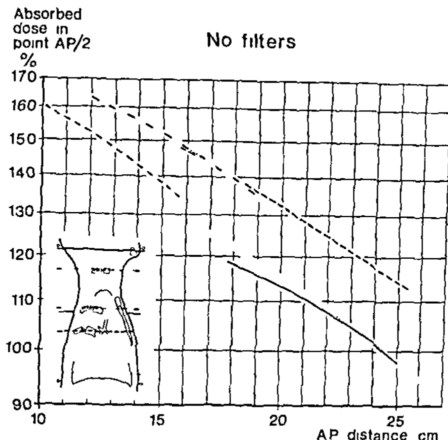


Fig 7 Absorbed dose in the sagittal section at point AP/2 at the levels of five transversal sections (I—II—III—IV fig 1 and at the level of Th12) as function of different a p distances in the sections No beam flattening filter was used Both fields received the same peak absorbed dose = 100 % AP = the anteroposterior distance AP/2 = the central point on the AP line

tion exposed with a catheter containing ionization chambers in the hypopharynx and the oesophagus After every fourth ionization chamber a lead cylinder was inserted to facilitate location of the chambers The shift in position of the oesophagus and even of the hila in relation to the spine will be apparent by a comparison of Fig 9a (supine position) and Fig 9b (prone), it amounted to about 3 cm at the level of Th9

The solid curves in Fig 10 indicate the absorbed dose along the hypopharynx and the oesophagus Caudally, where the oesophagus turns ventrally into the fundus ventriculi, the solid curves represent the absorbed dose along a line parallel to the spine The curves are based on dose plans in the sagittal section of six patients in the supine position In four of the patients the oesophagus moved on change of posture from the supine to the prone position, as illustrated in Fig 9 for patient A R The broken line in Fig 10 denotes the planned absorbed dose in the oesophagus after correction for such a shift of the oesophagus The ab-

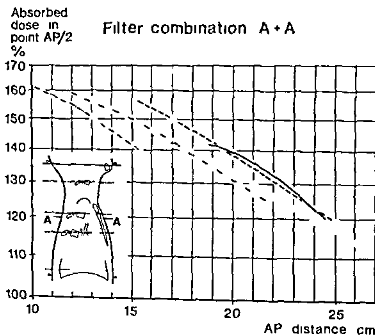


Fig 8 Absorbed dose in the sagittal section at point AP/2 at the levels of five transversal sections (I—II—III—IV fig 1 and at the level of Th12) as function of different a p distances in the sections Beam flattening filter was used Both fields received the same peak absorbed dose = 100 %

sorbed doses measured with condenser chambers in the hypopharynx and in the oesophagus are denoted by crosses in Fig 10 The crosses represent the mean value of two measurements during two treatments When one chamber was discharged the corresponding cross in Fig 10 denotes only one measurement If more than one third of the chambers in a catheter were discharged, another measurement was made in the patient

The patients in Fig 10 were chosen to represent a range of various anteroposterior distances The position of the catheters in relation to the trachea was determined by slow films exposed during treatment and to facilitate a comparison with the planned dose the measured values in Fig 10 were corrected for the presence of gas in the trachea According to phantom studies (SVAHN TAPPER 1970) this correction is — 7 % of the peak absorbed dose in the ventral field In the planned dose (solid and broken lines Fig 10) there is a variation of ± (1—2) % in the peak absorbed dose due to the area of the field Further, the sagittal sections of the patients are only approximate since they were drawn

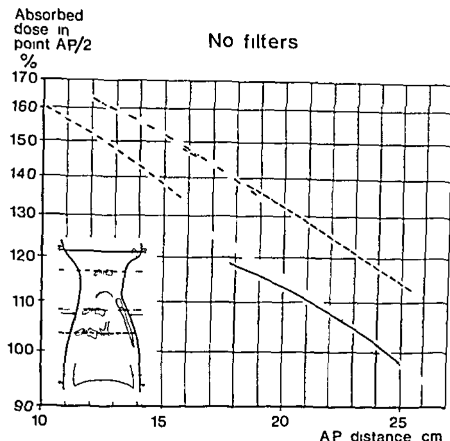


Fig 7 Absorbed dose in the sagittal section at point AP/2 at the levels of five transversal sections (I—II—III—IV fig 1 and at the level of Th12) as function of different a p distances in the sections No beam flattening filter was used Both fields received the same peak absorbed dose = 100 % AP = the anteroposterior distance AP/2 = the central point on the AP line

ion exposed with a catheter containing ionization chambers in the hypopharynx and the oesophagus After every fourth ionization chamber a lead cylinder was inserted to facilitate location of the chambers The shift in position of the oesophagus and even of the hila in relation to the spine will be apparent by a comparison of Fig 9a (supine position) and Fig 9b (prone), it amounted to about 3 cm at the level of Th9

The solid curves in Fig 10 indicate the absorbed dose along the hypopharynx and the oesophagus Caudally, where the oesophagus turns ventrally into the fundus ventriculi, the solid curves represent the absorbed dose along a line parallel to the spine The curves are based on dose plans in the sagittal section of six patients in the supine position In four of the patients the oesophagus moved on change of posture from the supine to the prone position, as illustrated in Fig 9 for patient A R The broken line in Fig 10 denotes the planned absorbed dose in the oesophagus after correction for such a shift of the oesophagus The ab-

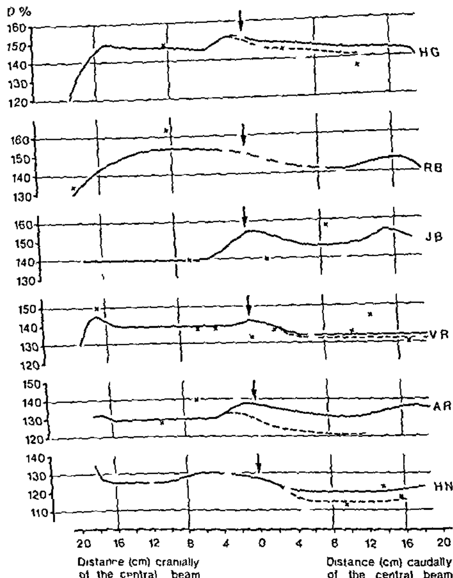


Fig 10 Absorbed dose (D) in *per cent* (*with 100 %* peak absorbed dose in the central beam in both the ventral and the dorsal fields) along the hypopharynx and the oesophagus in six patients The arrows *ind*cate the central beams The solid curves represent the planned absorbed dose and broken curves the planned dose in the oesophagus corrected for the effect of change in posture Crosses indicate the measured absorbed dose

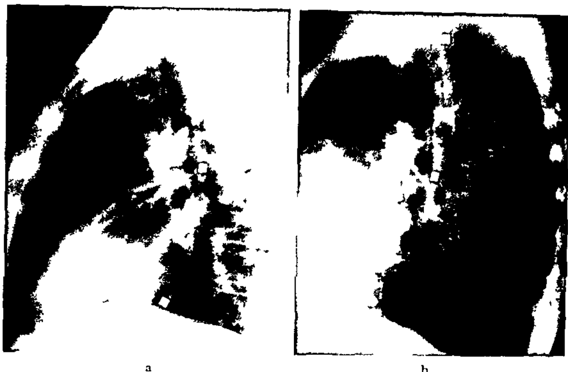


Fig 9 Roentgen films in supine (a) and prone (b) positions of the same patient A catheter containing ionization chambers and lead indicators has been passed into the oesophagus It may be observed that the oesophagus has shifted position the distance from the ventral border of the spine is longer in the prone than in the supine position (Cf patient A R in fig 10)

during routine clinical work The error is largest around the centre of the field and is due to the difficulty of preserving the contour of the patient on change of posture The use of plastic shells during treatment cannot eliminate this change in contour entirely Differences of as much as 2 cm were observed in the sagittal section, which means an error in the planned dose in the oesophagus of at most 7 % of the field peak absorbed dose All measurements in Fig 10 were obtained during routine clinical work and this means an error of up to ± 5 % of the measurements made with the condenser chambers The only correction for the effect of tissue inhomogeneity on the measurements was that for gas in the trachea

When using beam flattening filter and constructing the individual contour compensating filter for the neck, the aim was to get the maximum absorbed dose in the sagittal section between the level of the fourth rib posteriorly and the apices of the lungs, since between these levels there is (Fig 11) an accentuated minimum in absorbed dose lateral to the sagittal section

Most of the differences between planned and measured absorbed dose in the oesophagus could be explained Thus, in patient A R, control of the sagittal

Table

Absorbed dose measured laterally (= M) compared with the absorbed dose measured at the point AP/2 (= M_0) for two patients (J B and J I) The peak absorbed dose is 100 % in the central beam for both the ventral and the dorsal fields R = M/M_0 and should be compared with R in Fig 11

		Ventral						Dorsal					
		J B			J I			J B			J I		
		M	M_0	R	M	M_0	R	M	M_0	R	M	M_0	R
Position of condenser chambers	Supraclavicular fossa	147	140	1.05	140	145	0.97	146	140	1.04	156	150	1.04
		136	145	0.94	148	145	1.02	139	140	0.99	146	150	0.97
	Top of axilla	136	145	0.94	140	145	0.97	136	145	0.94	137	145	0.94
		138	145	0.95	133	150	0.89	136	145	0.94	140	145	0.97
	Middle and lower part of axilla	138	145	0.9	143	150	0.95	155	145	1.07	145	150	0.97
		139	145	0.96	144	145	0.99				160	150	1.07

For those patients in whom insertion of the catheter into the oesophagus proved technically difficult or impossible, the dose in the sagittal section was checked with measurements parallel to the spine on the front and back of the patient The oesophagus was checked after a barium swallow for any shift in position with roentgen films exposed in the two different treatment positions

Variation of absorbed dose in lateral direction Fig 11 is based on dose plans in the four cross sections (I—II—III—IV Fig 1) for ten patients The absorbed dose along the line OBA was normalized to the absorbed dose at point D (= AP/2) in the respective cross sections The size of the patient along the line OBA was normalized to that of an average subject The shaded areas represent the total variation in absorbed dose in lateral direction for the ten patients No correction for tissue inhomogeneity was made in the dose plans The true absorbed dose behind the mandible to the mastoid, especially where the beam passes almost tangentially through the corpus mandibulae was therefore smaller than that in the diagram for section I and the higher dose laterally in section I might therefore be an advantage In section II the larger dose in the lateral parts of the neck is localized to a region where lymph nodes are often involved in Hodgkin s disease In section III there is an accentuated minimum in absorbed dose at the top of the axilla The upper part of the axilla is a region where it is practically impossible to chart the spread of Hodgkin s disease and it seems to be im

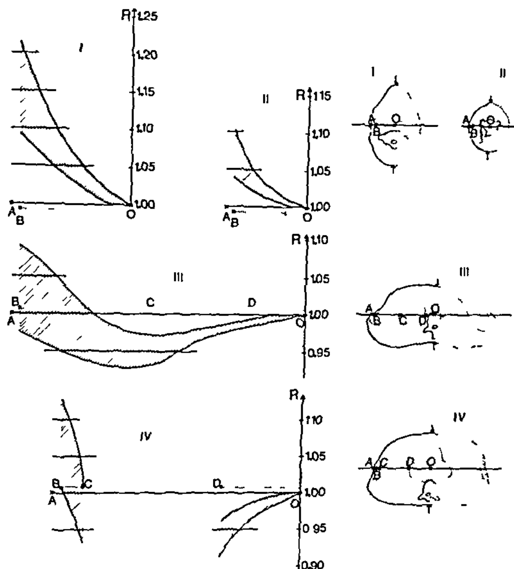


Fig 11 Quotient (R) between absorbed dose in the four transversal sections (I—II—III—IV fig 1) along lines perpendicular to the sagittal section through point 0 (AP/2) and absorbed dose at point 0 in ten patients No correction has been made for the presence of in homogeneous tissue Point A indicates the skin of the patient The length of line OA for the ten patients was normalized to that of an average subject The target is outlined by the dotted contours Points B C and D represent the borders of the target along the line 0A *Shaded areas cover the variation of R for the ten patients*

section showed that the patient had a larger a p distance caudally to the centre of the field than in the first sagittal section, further, the neck filter was recon structed in the region 3 to 9 cm cranial to the centre of the field For patient H G, the dosage in the caudal part of the mediastinum was determined accord ing to the measure figures as a precaution against underdosage

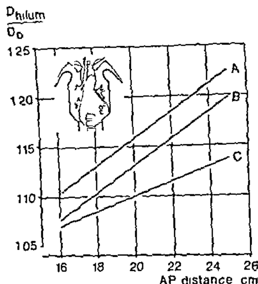


Fig 13 Variation of quotient D_{hilum} (= absorbed dose in the hilar region corrected for the presence of lung tissue) and D_0 (= absorbed dose at point 0 = point AP/2) as a function of different anteroposterior distances The thickness of the chest wall is 2 cm Both fields received the same peak absorbed dose The quotient is given for three different points Point A represents the region of maximum absorbed dose and has a theoretical width of about 1 cm Point B represents the lateral border of the hilum Point C corresponds to the same region as A but dorsal to the heart The heart is assumed to reduce the amount of lung tissue to two thirds along the local beam through C compared with the right side of the patient

applies to the axilla cranially to the level of the fourth rib posteriorly The results should be compared with the diagrams III and IV in Fig 11

Tissue inhomogeneity The presence of lung tissue in the hilar regions should be taken into account in planning a treatment Phantom investigations using sawdust with a density of 0 25 g/cm³ inside the chest wall produced a depth dose curve with a slope of 0 6 relative to water in a semilogarithmic plot (SVAHN—TAPPER 1970) Measurements of the exit absorbed dose at the level of the pulmonary hila in six patients with normal chest roentgenograms revealed that this quantity varied by 0 50 to 0 65 Since the measurements in these six patients were compatible with the results in the phantom studies, the value of 0 6 was used Fig 12 gives the dose distribution in the hilar regions (section IV) corrected for the presence of lung tissue for the same patient as in Fig 5 Fig 13 gives the quotient between the absorbed dose (D_{hilum}) at three different points of the hilar regions and the AP/2 dose (D_0) at the corresponding level plotted as a function of different a p distances In the calculations the chest wall was

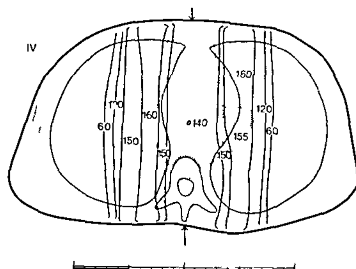


Fig 12 Dose distribution in section IV with corrections for the presence of lung tissue in the *hilar region (Cf with fig 5)*

portant to deliver an adequate absorbed dose to this region In the lateral parts of the axilla (section IV) the absorbed dose is larger than the corresponding AP/2 dose, but since it is difficult to preserve the patient contour in this region on change of posture from supine to prone, this larger dose is safeguard against underdosage *Slight overdosage in the axilla will probably have no serious side* effects The diagram for section IV illustrates the dose distribution in the hilar region without correction for the presence of lung tissue Individual correction for lung tissue in the hilar region is advisable in the treatment of patients

Comparison between planned and measured dose distribution in lateral direction The absorbed dose along the line OBA (Fig 11) cannot be controlled by measurements in patients Since there is only a small dose variation in a ventro-dorsal direction in the axillary region (cf with Fig 5) dose control can be replaced by measurements on the skin Catheters with condenser chambers were *placed on the patients as shown in Fig 3a This is exemplified in the* Table, where the absorbed dose (M) in the regions mentioned above is compared with the AP/2 dose (M_0) at the corresponding level in two of the patients For instance, for patient J B in the Table and in Fig 10, M_0 at the level of the central beam ± 4 cm can be approximated with the regression curve for the measurements in the oesophagus in this region, and is about 145 % The absorbed dose in the lateral parts of the supraclavicular fossa is almost the same as the AP/2 dose (Table) The absorbed dose in the upper part of the axilla is about 5 % smaller than the AP/2 dose at the corresponding level This smaller dose also

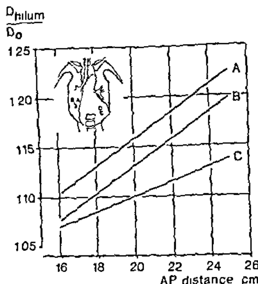


Fig 13 Variation of quotient D_{hilum} (= absorbed dose in the hilar region corrected for the presence of lung tissue) and D_0 (= absorbed dose at point 0 = point AP/2) as a function of different anteroposterior distances The thickness of the chest wall is 2 cm Both fields received the same peak absorbed dose The quotient is given for three different points Point A represents the region of maximum absorbed dose and has a theoretical width of about 1 cm Point B represents the lateral border of the hilum Point C corresponds to the same region as A but dorsal to the heart The heart is assumed to reduce the amount of lung tissue to two thirds along the local beam through C compared with the right side of the patient

applies to the axilla cranially to the level of the fourth rib posteriorly The results should be compared with the diagrams III and IV in Fig 11

Tissue inhomogeneity The presence of lung tissue in the hilar regions should be taken into account in planning a treatment Phantom investigations using sawdust with a density of 0 25 g/cm³ inside the chest wall produced a depth dose curve with a slope of 0 6 relative to water in a semilogarithmic plot (SVAHN—TAPPER 1970) Measurements of the exit absorbed dose at the level of the pulmonary hila in six patients with normal chest roentgenograms revealed that this quantity varied by 0 50 to 0 65 Since the measurements in these six patients were compatible with the results in the phantom studies the value of 0 6 was used Fig 12 gives the dose distribution in the hilar regions (section IV) corrected for the presence of lung tissue for the same patient as in Fig 5 Fig 13 gives the quotient between the absorbed dose (D_{hilum}) at three different points of the hilar regions and the AP/2 dose (D_0) at the corresponding level plotted as a function of different a p distances In the calculations the chest wall was

taken to be 2 cm thick Point A represents the maximum absorbed dose region, which has a theoretical width of about 1 cm Point B represents a point at the most lateral border of the hilum while point C represents a position in the left hilum dorsal to the heart The heart is assumed to reduce the amount of lung tissue to two thirds along the local beam through C, compared with the right side of the patient Curve C should be used instead of curve A if there are enlarged lymphomas in the hila but the density of the lung is normal With the cest wall 2 5 cm instead of 2 0 cm, the correction factors are approximately 1 % less

Absorbed dose in healthy tissues The total absorbed dose in the target varied from 3 900 to 4 500 rad over 9 weeks The absorbed dose in the spinal cord was 4 000 to 4 500 rad and in the caudal parts of the cerebellum it was 4 000 rad The absorbed dose measured in the auditory canal was about 3 500 rad The absorbed dose measured adjacent to the eyes varied between 0 and 120 rad Shielded lung tissue received an absorbed dose of about 700 rad

Conclusions

The agreement between planned and measured absorbed dose was good in all parts of the mantle field Any large differences could always be explained by a shift in position of viscera and other tissues on change of posture of the patient It was also found that both the number of dose plans and dose measurements can be reduced in the future

In the lateral direction, there is no need for beam flattening filters but it should be borne in mind that the absorbed dose is smaller at the top of the axilla than the AP/2 dose Dose planning in the cross sections is then not required and planning in the sagittal section is sufficient In the craniocaudal direction the use of a beam flattening filter is useful and the homogeneity of the absorbed dose can be further improved by combining the beam flattening filter with an individual filter compensating for the smaller a p distance in the neck region With this filter combination the variation in absorbed dose in the sagittal section was less than ± 10 % for all patients treated (and the variation in AP/2 dose less than ± 5 %) except in children, because children have a large a p distance in the submandibular region compared with distances in the rest of the treated volume To reduce the dose variation in the whole treatment volume, the maximum absorbed dose in the sagittal section should be placed between the level of the lung apices and the level of the fourth rib posteriorly because the dose is smallest laterally in this region The field width in the hilar regions must be reduced towards the end of the treatment period to secure the same absorbed dose in these regions as in the rest of the target

Dose measurements yield the greatest amount of information if performed in the hypopharynx and the oesophagus since these are situated almost in the centre of the patient and furthermore the absorbed dose then includes the effects of shifts in position of the viscera on change of po ture The absorbed dose should also be checked in the auditory canals to ensure that the nodes at the top of the mastoid receive adequate treatment

The technique and dosimetry of the mantle treatment with cobalt 60 could be improved by irradiating both fields with the patient only in supine position This would eliminate the shift in position of the viscera, which always reduces the absorbed dose (including that to the lymph nodes), while the dose to such healthy tissue as the spinal cord remains unchanged

SUMMARY

Patients with Hodgkin s disease were given mantle treatment with cobalt 60 The treat ment arrangement dose planning and dose measurements are described Methods for di minishing the variation in the absorbed dose in different parts of the target are discussed

ZUSAMMENFASSUNG

Die Mantelbestrahlung mittels Kobalt 60 wurde zur Behandlung der Hodgkinschen Er krankung benutzt Methodik Bestrahlungsplanung und Dosenmessungen werden beschrieben Es wird besprochen wie man eine Variation der Energiedosis im Zielgebiet vermeidet

RÉSUMÉ

Les auteurs ont traite des malades atteints de maladie de Hodgkin par irradiation en mantelet au moyen du cobalt 60 Ils decrivent les modalités du traitement le plan de dose et les mesures de dose Ils etudient les methodes destinées a diminuer les differences de dose absorbee dans les differentes parties du volume cible

REFERENCES

ANDERSON R E D ANGIO G J and KHAN F M Dosimetry of irregularly shaped radiation therapy fields Part I Some factors influencing inhomogeneity Part II Isodose contours obtained utilizing a simulated human thorax Radiology 92 (1969), 1092

CLARKSON L F A note on depth doses in fields of irregular shape Brit J Radiol 14 (1941) 265

CRAVER L F Some aspects of the treatment of Hodgkin s dissease Cancer 7 (1954) 927

DUTREIX A et DUTREIX J Construction des isodoses pour les surfaces obliques et irrégulières J Radiol 43 (1967) 671

EASSON E C and RUSSEL M H The cure of Hodgkin s disease Brit med J 1963 I p 1704

FULLER L M Results of intensive regional radiation therapy in the treatment of Hodgkin s disease and the malignant lymphomas of the head and neck Amer J Roentgenol 99 (1967) 340

— JING B S, SHULLENBERGER C C and BUTLER J J Radiotherapeutic management of localised *Hodgkin s disease involving the mediastinum* Brit J Radiol 40 (1967) 913

GILBERT R Le traitement de la granulomatose maligne par la roentgenthérapie pénétrante Acta radiol 9 (1928), 552

JELLIFFE A M *The present place of radiotherapy in the cure of Hodgkin s disease* Clin Radiol 16 (1965) 274

— and THOMSON A D The prognosis in Hodgkin s disease Brit J Cancer 9 (1955) 21

KAPLAN H S The radical radiotherapy of *regionally localized Hodgkin s disease* Radiology 78 (1962) 553

— Evidence for a tumoricidal dose level in the radiotherapy of Hodgkin s disease Cancer Res 26 (1966) 1221

— Role of intensive radiotherapy in the management of Hodgkin s disease Cancer 19 (1966), 356

— Prognostic significance of the relapse free interval after radiotherapy in Hodgkin s disease Cancer 22 (1968) 1131

— and ROSENBERG S A The treatment of Hodgkin s disease Med Clin N Amer 50 (1966), 1591

— — Extended field radical radiotherapy in advanced Hodgkin s disease short term results of 2 randomized clinical trials Cancer Res 26 (1966) 1268

LANDBERG T Clinical course of Hodgkin s disease treated with radiotherapy Acta radiol Ther Phys Biol 8 (1969) 487

— und LARSSON L E Studium des klinischen Verlaufs bei Sternbergscher Erkrankung Radiol Austr 19 (1968) 197

— — Hodgkin s disease Retrospective clinicopathologic study in *149* patients Acta radiol Ther Phys Biol 9 (1969) 390

MEURK M L GREEN J P NUSSBAUM H and VAETH J M Phantom dosimetry study of shaped *Cobalt 60 fields in the treatment of Hodgkin s disease Radiology 91 (1968)* 554

MUSSHOFF K und BOUTIS L Die Frage der Heilbarkeit der Lymphogranulomatose beurteilt nach den Behandlungsergebnissen der Freiburger Medizinischen Klinik Verhandlungen der Deutschen Gesellschaft für innere Medizin 73 Kongress 1967 XLV 322 Verlag J F Bergmann Munchen 1967

— — Therapy results in Hodgkin s disease Cancer 21 (1968) 1100

NEWALL J The management of Hodgkin s disease Clin Radiol 16 (1965) 40

NICE C M and STENSTROM K W Irradiation therapy in Hodgkin s disease Radiology 62 (1954) 641

NOBLER M P Curative radiotherapy in the malignant lymphomas Cancer 22 (1968) 752

PATERSON R and PATERSON E Hodgkin s disease Brit med J 1954 II p 1315

PETERS M V A study of survivals in Hodgkin s disease treated radiologically Amer J Roentgenol 63 (1950) 299

— Prophylactic treatment of adjacent areas in *Hodgkin s disease Cancer Res 26 (1966)*, 1232

— and MIDDLEMISS K C H A study of Hodgkin s disease treated by irradiation Amer J Roentgenol *79 (1958) 114*

PUSEY W A Case of sarcoma and of Hodgkin s treated by exposures to X rays — a preliminary report J Amer med Ass 38 (1902) 166

ROSENBERG S A Report of the committee on the staging of Hodgkin s disease Cancer Res 26 (1966) 1310

— and KAPLAN H S Evidence for an orderly progression in the spread of Hodgkin s disease Cancer Res 26 (1966) 1225

RUBIN P and KUROHARA S S Has prophylactic irradiation proved itself in the treatment of localized Hodgkin s disease? Radiology 87 (1966) 240
SALZMAN F A SMEDAL M I WRIGHT K A and TRUMP J G Two MeV wide field irradiation of lymphoma Amer J Roentgenol 92 (1964) 124
SCHEER A C The course of stage I malignant lymphomas following local treatment Amer J Roengenol 90 (1963) 939
SMITHERS D W Factors influencing survival in patients with Hodgkin s disease Clin Radiol 20 (1969) 124
STRICKSTROCK K H MUSSHOFF K und BOUTIS L Methode der zusatzlichen prophylaktischen Bestrahlung bei der Lymphogranulomatose Strahlentherapie 133 (1967) 337
SVAHN TAPPER G Dosimetric studies of mantle fields in cobalt 60 therapy of malignant lymphomas Acta radiol Ther Phys Biol 9 (1970) 190
WESTLING P Studies of the prognosis in Hodgkin s disease Acta radiol (1965) Suppl No 245

— JING B S, SHULLENBERGER C C and BUTLER J J Radiotherapeutic management of localised Hodgkin s disease involving the mediastinum Brit J Radiol 40 (1967), 913

GILBERT R Le traitement de la granulomatose maligne par la roentgenthérapie pénétrante Acta radiol 9 (1928) 552

JELLIFFE A M The present place of radiotherapy in the cure of Hodgkin s disease Clin Radiol 16 (1965) 274

— and THOMSON A D The prognosis in Hodgkin s disease Brit J Cancer 9 (1955) 21

KAPLAN H S The radical radiotherapy of regionally localized Hodgkin s disease Radiology 78 (1962) 553

— Evidence for a tumoricidal dose level in the radiotherapy of Hodgkin s disease Cancer Res 26 (1966), 1221

— Role of intensive radiotherapy in the management of Hodgkin s disease *Cancer* 19 (1966) 356

— Prognostic significance of the relapse free interval after radiotherapy in Hodgkin s disease Cancer 22 (1968) 1131

— and ROSENBERG S A The treatment of Hodgkin s disease Med Clin N Amer 50 (1966) 1591

— — Extended field radical radiotherapy in advanced Hodgkin s disease short term results of 2 randomized clinical trials Cancer Res 26 (1966) 1268

LANDBERG T Clinical course of Hodgkin s disease treated with radiotherapy Acta radiol Ther Phys Biol 8 (1969) 487

— und LARSSON L E Studium des klinischen Verlaufs bei Sternbergscher Erkrankung *Radiol Austr 19 (1968), 197*

— — Hodgkin s disease Retrospective clinicopathologic study in 149 patients Acta radiol Ther Phys Biol 9 (1969), 390

MEURK M L GREEN J P NUSSBAUM H and VAETH J M Phantom dosimetry study of shaped Cobalt 60 fields in the treatment of Hodgkin s disease Radiology 91 (1968) 554

MUSSHOFF K und BOUTIS L Die Frage der Heilbarkeit der Lymphogranulomatose beurteilt nach den Behandlungsergebnissen der Freiburger Medizinischen Klinik Verhandlungen der Deutschen Gesellschaft fur innere Medizin 73 Kongress 1967 XLX 322 Verlag J F Bergmann Munchen 1967

— — Therapy results in Hodgkin's disease Cancer 21 (1968) 1100

NEWALL J The management of Hodgkin s disease Clin Radiol 16 (1965) 40

NICE C M and STENSTROM K W *Irradiation therapy in Hodgkin s disease Radiology 62* (1954) 641

NOBLER M P Curative radiotherapy in the malignant lymphomas Cancer 22 (1968) 752

PATERSON R and PATERSON E *Hodgkin s disease Brit med J 1954 II p 1315*

PETERS M V A study of survivals in Hodgkin s disease treated radiologically Amer J Roentgenol 63 (1950) 299

— Prophylactic treatment of adjacent areas in Hodgkin s disease Cancer Res 26 (1966), *1232*

— and MIDDLEMISS K C H A study of Hodgkin s disease treated by irradiation Amer J Roentgenol 79 (1958) 114

PUSEY W A Case of sarcoma and of Hodgkin s treated by exposures to X rays — a preliminary report J Amer med Ass *38 (1902) 166*

ROSENBERG S A Report of the committee on the staging of Hodgkin s disease Cancer Res 26 (1966) 1310

— and KAPLAN H S Evidence for an orderly progression in the spread of Hodgkin s disease Cancer Res 26 (1966) 1225

Table 1

Dosimetric systems applied by the different laboratories involved in the intercomparisons

Röntgen und Strahleninstitut Abt. für Strahlungsphysik Rudolf Virchow-Krankenhaus Berlin	Radiation Physics Department University of Umeå Umeå	Gesellschaft für Strahlenforschung Abt. für Biophysikalische Strahlenforschung Frankfurt/Main
Barrel ionization chamber calibrated by PTB Braunschweig BRD at 250 kV used for determination of J_g	*Calorimeter* (ref. 12) for determination of G value of ferrous sulphate with electron radiation	*Extrapolation ionization chamber* (ref. 17) compared with a standard Faraday cage (ref. 6) and with a total absorbing calorimeter (ref. 14)
↓	↓	↓
Ionization chambers (ref. 20) used for determination of J_g and calculation of absorbed dose at electron radiation (comparison with absorbed dose determined with ferrous sulphate)	*Ferrous sulphate dosimeter* (ref. 13 and 18) for absorbed dose calibration of thimble chambers at different electron energies and depths in water phantom	*Standard ionization chamber* (ref. 15) for determination of absorbed dose in dose maximum and depth ionization curves
	↓	
	Thimble chambers (ref. 4 and 18) for determination of absorbed dose in dose maximum and depth dose curves	
Intercomparisons in Berlin BBC 35 MeV		Intercomparisons in Frankfurt/Main Siemens 35 MeV

Berlin The absorbed dose in water D_{H_2O} was determined by the following relation

$$D_{H_2O} = \frac{W}{e} \; S(E_d) \; J_g \tag{1}$$

where

- W is the mean energy spent for the production of one ion pair
- e is the charge of the positron
- $S(E_d)$ is a function of the electron energy E_d at the depth d in a water phantom — the values of $S(E_d)$ chosen were the means of the experimental and calculated values determined by HARDER (1965) respectively MARKUS (1964)
- J_g is the quotient of the ionization charge and the mass of the gas ICRU Report No 14 (1969)

FROM THE RADIATION PHYSICS DEPARTMENT (PROF G HETTINGER), UNIVERSITY OF UMEA, SWEDEN, ABT FUR STRAHLUNGSPHYSIK (PROF D FROST), RONTGEN UND STRAHLENINSTITUT, RUDOLF VIRCHOW KRANKENHAUS, BERLIN, AND ABT FUR BIOPHYSIKALISCHE STRAHLENFORSCHUNG (PROF W POHLIT), GESELLSCHAFT FUR STRAHLENFORSCHUNG, FRANKFURT/MAIN, DEUTSCHLAND

INTERCOMPARISONS OF ABSORBED DOSE DETERMINATIONS IN 10 TO 35 MeV ELECTRON RADIATION

by

H Svensson, G Hettinger, D Frost and W Pohlit

There are as yet no recommendations from ICRU concerning standardized measurements of the dose in a tissue equivalent phantom at high energy electron radiation Different dosimetric systems or combinations of systems are used in different laboratories In this paper, an intercomparison between the dosimetric techniques developed and used by the groups in Berlin, Frankfurt/Main and Umea, respectively, are described

Determinations of absorbed dose in dose maximum and of relative depth dose curves in a water phantom were compared The measurements were carried out using the betatrons in Berlin and Frankfurt/Main

Dosimetric systems

The independent dosimetric systems applied by the three laboratories are presented in Table 1 A more detailed description is given below

This work was supported by grants from the Swedish Cancer Society Submitted for publication 16 February 1970

Another comparison has been made by measuring the energy fluence Ψ with a total absorbing calorimeter (POHLIT 1964) and using

$$D_{H_2O} = (dE/\varrho dx)_{H_2O} \frac{\Psi}{\bar{E}_e} \tag{6}$$

The energy of the electrons $\bar{E}_e$ has been determined by photonuclear reaction (POHLIT 1969).

The three absorbed dose determinations agreed within ± 2 %. For practical dosimetry thimble chambers, the Fricke dosimeter (LIESEM & POHLIT 1962) and thermoluminescence dosimeters were calibrated with the standard extrapolation chamber.

A simpler sub-standard ionization chamber (POHLIT 1965) has been constructed with the same geometrical data as the extrapolation chamber. This instrument was used in all experiments described in this paper.

Umeå. The ionization chambers used for the intercomparison, were calibrated against ferrous sulphate dosimeters. The G-value of the ferrous sulphate dosimeter was initially determined by a calorimetric technique. A short summary of the different stages in the calibration procedure follows.

The integrated absorbed dose in a water volume was measured absolutely with a liquid calorimeter (PETTERSSON 1967). This dose information was used to determine the G-value for the ferrous sulphate dosimeter (0.4 M) at a mean electron energy of about 20 MeV. The G-value was determined as 0.1596 ± 0.0012 (standard error) eV^{-1} at 25° C irradiation temperature. A molar extinction coefficient of ferric ions at 304 nm equal to 2.196 · 10^3 liters · mol^{-1} · cm^{-1} at 25° C was used. The absorbed dose in water was estimated to be 0.4 % higher than in the ferrous sulphate dosimeter solution. A more detailed description of the ferrous sulphate dosimetry used has been given by PETTERSSON & HETTINGER (1967).

For the measurement of depth dose curves, as many as 20 irradiation cells of polystyrene were placed in succession in a water phantom. The sensitivity of the dosimeters was assumed to be independent of phantom depth and electron energy in the range 5—30 MeV. Possible influences of storage time and cell material on chemical response were taken into account (SVENSSON et coll. 1967). The measured depth dose curves were used to calibrate thimble chambers in rad (H_2O) per scale division at different electron energies and phantom depths.

Relative depth ionization curves measured with thimble chambers of different sizes agreed provided the effective point of measurement was chosen to be 3/4 r in front of the centre of the chamber, where r is the radius of the chamber cavity (HETTINGER et coll. 1967).

The incident energy of the electrons at the phantom surface E_0 [MeV] was determined from the energy range relation (POHLIT 1965)

$$R_{max_{Al}} = C_1 \cdot E_0 \tag{2}$$

where

$C_1 = 0.246$ MeV^{-1} · cm

$R_{max\,Al}$ (cm Al) is the maximum range of electrons in aluminium

E_d was related to the energy E_0 by the relation (HARDER 1965)

$$E_d = E_0 \left(1 - \frac{d}{R_p}\right) \tag{3}$$

where

R_p (cm H_2O) is the practical extrapolated range determined from depth dose curves in water at large field sizes.

J_g was measured with a selfconstructed ionization chamber (WURTNER & FROST 1962) and with a Radocon Model 575 A thimble ionization chamber connected to a Victoreen electrometer. Both instruments were calibrated at 250 kV against a barrel chamber (Kustner Eich-Standgerat) in connection with a dc-amplifier as reference. The barrel chamber together with the dc-amplifier were calibrated by the PTB (Physikalich Technische Bundesanstalt) Braunschweig, BRD.

The absorbed dose was also determined employing ferrous sulphate (0.4 M) dosimetry. The molar extinction coefficient of ferric ions at 304 nm was determined as 2.198 · 10^3 liters · mol^{-1} · cm^{-1} at 25° C (spectrophotometer PMQII Carl Zeiss). A G-value of 0.156 eV^{-1} was used.

The difference between the absorbed dose determinations with the ionization and with the ferrous sulphate method was less than 2 %.

Frankfurt/Main. For the calibration of practical dosimeters an extrapolation ionization chamber has been developed as a standard instrument (RASE & POHLIT 1962) for the measurement of the quantity J_g in the Bragg-Gray relation

$$D_{H_2O} = \frac{(dE/\varrho dx)_{H_2O}}{(dE/\varrho dx)_{air}} \cdot \frac{W}{e} \cdot J_g \tag{4}$$

where

$dE/\varrho \cdot dx$ is the mass stopping power, W is the mean energy spent for the production of one ion pair in air and e is the charge of the positron. This instrument has been compared with a standard Faraday cage (KRETSCHKO et coll. 1962) where the absorbed dose was determined from the particle fluence Φ by

$$D_{H_2O} = (dE/\varrho dx)_{H_2O} \cdot \Phi \tag{5}$$

ionization curves in water at large field sizes (LOEVINGER et coll 1961 MARKUS 1961 and 1964 NUSSE 1969)

The mean energy of the primary electrons E_m at the effective point of measurement was determined from the relation (compare with eq 2)

$$E_m = F_o\left(1 - \frac{d}{R_p}\right) \tag{8}$$

where

d (cm H_2O) is the effective measurement depth (HARDER 1965)

Intercomparison measurements and instrumentation

Berlin The intercomparisons were carried out with a 35 MeV betatron Brown Boveri Asklepitron 35 at SSD 110 cm and at 25 30 and 35 MeV according to the panel MeV meter reading The electrons leave the accelerator tube through about 4 mm of glass and then pass through a scattering foil of about 0 4 mm Cu All intercomparison measurements were referred to the transmission monitor chamber

A Baldwin Farmer X ray dosimeter (0 6 cm^3 ionization chamber) a Siemens Sondenfingerhutkammer connected to a Townsend coupling a 30 cm × 30 cm × 30 cm water phantom and an automatic device for moving the ionization chamber were brought from Umea The ionization chambers which were dose calibrated in Umea were checked before and after the journey From the depth ionization curves measured in Berlin the incident energy of the electrons at the phantom surface was determined (eq 7) The mean energy of the primary electrons at the measurement depth was calculated (eq 8) in order to determine the relevant dose calibration factor of the ionization chamber used Absorbed dose at dose maximum in water per betatron monitor scale division, as well as depth dose curves were calculated from the measured depth ionization curves

Frankfurt/Main The intercomparison measurements were carried out with a 35 MeV betatron (Siemens A G Erlangen BRD) The electron beam leaves the accelerator tube through a window closed by a 0 1 mm thick aluminium foil No scattering foil was used in these experiments During all measurements two transmission chambers were in use for monitoring the fluence rate and fluence of the electron beam The collected charge of the fluence monitor and of the substandard ionization chamber were compensated by the Townsend method Alternatively the compensation voltage was measured with an electronic digital voltmeter The reproducibility of the measurements was within the 0 1 % limit

Table 2

Results of intercomparison measurements of absorbed dose in dose maximum along the central ray

Betatron	Panel MeV meter	Field size (cm)	Absorbed dose in water (rad) at dose maximum per monitor scale division as measured by: Berlin group	Umeå group	Frankfurt/Main group	Difference (%)
BBC 35 MeV Berlin	25	⌀ 8	0.877	0.800		9.6
		8×10	0.877	0.805		8.9
		14×14	0.885	0.781		13.3
	30	14×14	0.769	0.763		0.8
	35	⌀ 8	0.833	0.847		—1.7
		8×10	0.833	0.859		—3.1
		14×14	0.833	0.819		1.7
Siemens 35 MeV	14	⌀ 12		5.00	5.13	2.6
Frankfurt am Main	24	⌀ 12		4.72	4.82	2.1
	29	⌀ 12		4.67	4.73	1.3

Dose calibration factors of the thimble chambers were obtained by determining the ratio, at different phantom depths, between depth dose measured with ferrous sulphate dosimeters and depth ionization determined with thimble chambers. The dose calibration factors at the effective depth of measurement, d, depended on the mean energy of the primary electrons, E_m. E_m was calculated according to equations (7) and (8). Other parameters of the radiation field such as field size (larger than ⌀ 5 cm), SSD (between 110—130 cm), and construction of the collimating system had, however, no significant influence on the factors (SVENSSON & PETTERSSON 1967). Measurements of dose calibration factors made with 10 betatrons in the Scandinavian countries gave the same result independent of with which betatron the measurements were carried out.

The incident energy of the electrons at the phantom surface E_0 [MeV] was determined from the energy range relation (compare with eq. 2)

$$R_p = k_1 \cdot E_0 - k_2 \qquad (7)$$

where

$k_1 = 0.52 \text{ MeV}^{-1} \cdot \text{cm}$

$k_2 = 0.3$ cm

R_p (cm H_2O) is the practical extrapolated range determined from depth

values measured with the Frankfurt/Main betatron by the Frankfurt and Umea groups at 14 24 an 29 MeV were between 1 and 3 %

Depth dose curves for 25 and 35 MeV on the Berlin betatron are shown in Fig 1 The agreement appears to be acceptable when the distributions are used for radiotherapy An intercomparison of depth ionization curve measured with the Frankfurt/Main betatron at 14 and 29 MeV is shown in Fig 2 There were no discrepancies between the results from the two groups In the same figure relative depth dose curves are also given These were calculated from the depth ionization curves according to the method used by the Umea group

This intercomparison shows that well equipped laboratories are able to perform the determination of absorbed dose of fast electrons with different methods and with suitable accuracy for medical use However the difficulties observed in these measurements indicate the urgent need of international agreement on common quantities and procedures of measurements

SUMMARY

Dosimetric intercomparisons between Berlin and Umea and between Frankfurt/Main and Umea were performed using electron radiation The mea urements were carried out on betatrons in Berlin and in Frankfurt/Main Compared with the Umea calibrations one betatron at 25 MeV showed a difference of about 10 % in the measured absorbed dose at the dose maximum For the other seven calibrations at different field sizes and energies Berlin was on the average about 2 % below and Frankfurt/Main on the average about 2 % above the Umea calibrations

ZUSAMMENFASSUNG

Dosimetrische Vergleiche von Elektronen Strahlung zwischen Berlin und Umea und Frankfurt/Main und Umea wurden durchgefuhrt Die Messungen wurden an Betatrons in Berlin und Frankfurt/Main vorgenommen Verglichen mit den Kalibrierungen in Umea fand sich eine Differenz fur ein Betatron bei 25 MeV von etwa 10 % fur die gemessene absorbierte Dosis bei dem Dosis Maximum Fur die anderen sieben Kalibrierungen bei verschiedenen Feldgrossen und Energien lag Berlin durchschnittlich etwa 2 % unter und Frankfurt/Main durchschnittlich 2 % uber den Kalibrierungen von Umea

RÉSUMÉ

Les auteurs ont fait des comparaisons de dosimétrie entre les appareillages de Berlin et de Umeå et entre Frankfort sur le Main et Umeå en utilisant le rayonnement électronique Les mesures ont ete faites sur des betatrons à Berlin et à Frankfort sur le Main Compare a l etalonnage d Umeå un betatron presentait à 25 MeV une difference d environ 10 % sur la dose absorbee à la dose maximum Pour les sept autres etalonnages faits avec differentes dimensions de champs et differentes energies les mesures de Berlin étaient en moyenne inférieures d environ 2 % et celles de Frankfort sur le Main en moyenne superieures de 2 % aux etalonnages d Umea

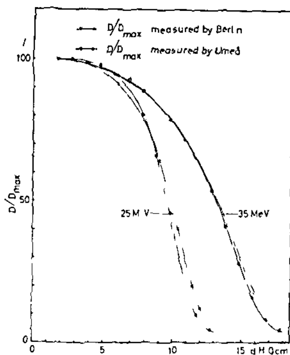


Fig 1

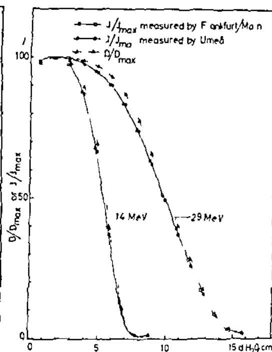


Fig 2

Fig 1 Relative absorbed dose D/D_{max} as a function of depth in water d_{H_2O} measured by Berlin group and by Umeå group at the betatron in Berlin The field size was 14 cm × 14 cm and the energies refer to the reading of the panel MeV meter

Fig 2 Relative mass ionization J/J_{max} as a function of depth in water d_{H_2O} measured by Frankfurt/Main group and by Umeå group at the betatron in Frankfurt/Main Values for relative absorbed dose D/D_{max} for water are calculated according to the method used by the Umeå group The field size was Ø 12 cm and the energies refer to the reading of the panel MeV meter

The measurements by the *Umea group in Frankfurt/Main* were carried out in the same way as in Berlin

Results and Discussion

The results of intercomparison measurements of dose in dose maximum in water along the central ray are shown in Table 2 The absorbed dose values in rad (H_2O) per betatron monitor scale division determined in Berlin by the Berlin and Umea groups differed by a few percent at 30 and 35 MeV At 25 MeV, however, a systematic difference was found, amounting to about 10 % This difference was probably due to an occasional instability of the extraction steering at 25 MeV (FROST & WURTHNER 1964) For this reason the Berlin values at

FROM THE DEPARTMENTS OF SURGERY II (DIRECTOR PROF R ROMANUS) PATHOLOGY II (DIRECTOR PROF S RANSTROM) RADIOTHERAPY (DIRECTOR PROF M STRANDQVIST), ROENTGENDIAGNOSTIC DEPARTMENT II (DIRECTOR PROF I WICKBOM) AND DEPARTMENT OF RADIOPHYSICS (DIRECTOR ASSOC PROF H SKOLDBORN), GOTHENBURG, SWEDEN

TOPOGRAPHY OF LYMPH DRAINAGE FROM MAMMARY GLAND AND HAND TO AXILLARY LYMPH NODES

by

A HULTBORN, L HULTEN B ROOS M ROSENCRANTZ, B ROSENGREN and CH ÅHREN

Two main techniques have been adopted in recent years in studying the lymph drainage of the breast in vivo The use of radioactive tracers in assessing the lymph drainage from the breast to the axillary internal mammary and supraclavicular nodes has been described by HULTBORN & JONSSON (1955), HULTBORN et coll (1955) and TURNER WARWICK (1959) Lymphography, i e injection of oily contrast media into lymph vessels on the dorsum of the hand has made it possible to demonstrate the axillary lymph nodes The same method has also been applied in the preoperative assessment of axillary lymph node metastases from carcinoma of the breast (KENDALL et coll 1963 and HULTEN et coll 1966) The distribution of a radioactive tracer injected locally into the breast parenchyma is supposed to reflect the natural lymph flow

Lymphography from the hand has been criticized on the grounds that lymph

Submitted for publication 9 January 1970

REFERENCES

1 FROST D und WÜRTHNER K Über die Beeinflussung des Rontgenstrahlungsuntergrundes in der Elektronenstrahlung eines 35 MeV Betatrons Strahlentherapie 124 (1964), 513

2 HARDER D *Berechnung der Energiedosis aus Ionisationsmessungen bei Sekundarelektronen Gleichgewicht* *In* Symposium on High Energy Electrons Edited by A Zuppinger and G Poretti Springer Verlag Berlin 1965

3 — Energiespektren schneller Elektronen in verschiedenen Tiefen *In* Symposium on High Energy Electrons Edited by A Zuppinger and G Poretti Springer Verlag Berlin 1965

4 HETTINGER G, PETTERSSON C and SVENSSON H Displacement effect of thimble chambers exposed to a photon or electron beam from a betatron Acta radiol Ther Phys Biol 6 (1967), 61

5 ICRU Report 14 Radiation Dosimetry X Rays and Gamma Rays with Maximum Photon Energies Between 0 6 and 50 MeV *ICRU, Washington 1969*

6 KRETSCHKO J HARDER D und POHLIT W Absolutmessung der Teilchenflussdichte schneller Elektronen mit einem Faraday Kafig Nucl Instr and Methods 16 (1962) 29

7 LIESEM H und POHLIT W Dosismessungen an schnellen Elektronen nach der Eisensulfatmethode Zeitschr Phys Chem 35 (1962) 3.2

8 LOEVINGER R KARZMARK C J and WEISSBLUTH M Radiation therapy with high energy electrons Part I Physical considerations 10 to 60 MeV Radiology 77 (1961) 906

9 MARKUS B Energiebestimmung schneller Elektronen aus Tiefendosiskurven Strahlentherapie 116 (1961) 280

10 — Beitrage zur Entwicklung der Dosimetrie schneller Elektronen Teile I II und III Strahlentherapie 123 (1964) 350 508 124 (1964) 33

11 NÜSSE M Factors affecting the energy range relation of fast electrons in aluminium *Phys Med Biol 14 (1969) 315*

12 PETTERSSON C Calorimetric determination of the G value of the ferrous sulphate dosimeter with high energy electrons and Co 60 gamma rays Arkiv Fysik 34 (1967) 385

13 — and HETTINGER G Dosimetry of high energy electron radiation based on the ferrous sulphate dosimeter Acta radiol Ther Phys Biol 6 (1967) 160

14 POHLIT W Absolute Messung energiereicher Bremsstrahlung Wiss Z Univ Jena 13 (1964) 523

15 — Dosimetrie zur Betatrontherapie Thieme Verlag Stuttgart 1965

16 — Energy calibration of betatron X rays and electrons up to 40 MeV Ann N Y Acad Sci 161 (1969) 119

17 RASE S und POHLIT W *Eine Extrapolationskammer als Standardmessgerat für energie*reiche Photonen und Elektronenstrahlung Strahlentherapie 119 (1962) 266

18 SVENSSON H and PETTERSSON C Absorbed dose calibration of thimble chambers with high energy electrons at different phantom depths Arkiv Fysik 34 (1967) 377

19 — — and HETTINGER G Effects on ferrous sulphate dosimeter solution stored in small polystyrene cells *In* Solid state and chemical radiation dosimetry in medicine and biology IAEA Vienna 1967

20 WÜRTHNER K und FROST D Über die Entwicklung eines *Korperhohlendosimeters für* schnelle Elektronen DFG Forschungsbericht Aktenzeichen Fr 171/1 Kennwort Korperhohlendosimeter 1962



Fig 2 a) Ventral layer of specimen lymphadenogram b) Dorsal layer

Lymphography was performed by the intralymphatic injection of 6 to 8 ml Lipiodol 38 % into the dorsum of the hand The axillary and supraclavicular regions were examined roentgenographically immediately after the injection and 24 hours later A full description of the procedure has been given in a previous paper (HULTBORN et coll 1970)

Operation The patients were subjected to radical mastectomy and axillary dissection according to Halsted and subsequently Meyer, although the operation was especially modified for the investigation The breast and both pectoral muscles were removed en bloc and the axillary lymph node dissection was postponed to a later phase of the operation The major vessels and nerve trunks were stripped free from surrounding tissue at the axillary dissection The tissues in the infraclavicular region and those in the angle between the axillary vessels and first rib were meticulously dissected out The fascia and fatty tissue were removed from the anterior surface of the anterior serratus, subscapular and teres major mu cles The subscapular vessels and the cranial part of the anterior sheath of the rectal muscle were taken away

In two of the patients the axillary tissue was removed without further attempts to identify the contained lymph nodes anatomically

In order to facilitate the later topographic orientation of each individual node in the specimen more exactly, silver clips or steel wire sutures were in six patients affixed at certain positions corresponding to the axillary vein the thoracic wall and the subscapular vessels In four of these patients the axillary lymph nodes were dissected by a two-phase procedure the first including the nodes at the superficial or ventral level the second the deep or dorsal groups of lymph nodes (Fig 2)

When lymph node dissection according to either procedure was concluded

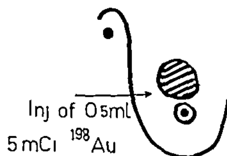


Fig 1 Sites of tumour and of ^{198}Au injection

nodes revealed by this route of injection are probably not wholly identical with the nodes that drain the breast

It has also been proposed from a clinical point of view that selective removal of axillary lymph nodes, *i e those draining the breast, and sparing the others,* would be of great advantage in operations for mammary carcinoma, since post operative sequelae such as lymphoedema, erysipelas and disturbances of the function of the arm might be reduced Since this question is of considerable importance, we have studied the lymph drainage from the hand and from the breast by combining the injection of a radioactive tracer into the breast and lymphography from the hand This method has been described in a previous paper (HULTBORN et coll 1970) and has been applied in patients awaiting radical mastectomy for carcinoma of the breast

The purpose of the present investigation was to find out whether a radioactive tracer injected locally into the breast parenchyma would be distributed to regional lymph nodes in the axilla other than those revealed by lymphography from the dorsum of the hand, or whether the tracer and the contrast medium might be similarly distributed to the axillary nodes

Eight patients with clinical, roentgenologic and cytologic signs of mammary carcinoma but no clinical evidence of metastases in the axilla were investigated The procedure was as follows injection of a tracer substance (^{198}Au) *into the* parenchyma of the breast, followed the next day by lymphography with Lipiodol (the reason for this sequence was that this medium may impede the introduction of the ^{198}Au), radical mastectomy and postoperative investigation of the specimen including roentgen examination directed to the contrast medium, measurement of the radioactivity, autoradiography and finally histologic examination

Tracer investigation A colloidal suspension of metallic ^{198}Au was injected with a fine needle into the breast parenchyma (Fig 1), in amounts of 0 5 to 1 5 ml and 1 5 to 5 0 mCi (HULTBORN et coll 1970)



Fig 3 a) Lymphadenogram before radical mastectomy Axillary and supraclavicular lymph nodes containing Lipiodol a few lymph vessels and extravasated contrast medium lie in the axilla b) Examination after radical mastectomy with all axillary nodes containing Lipiodol removed but with nodes *in the supraclavicular* region beyond the operation field remaining

Individual nodes thus identified in the postoperative specimen lymphadenogram could be transferred to a diagram and for practical purposes arranged *in conventional* groups Furthermore in four of these cases lymph nodes located in a ventral layer of the axillary fat could be separated from those in a dorsal *(scapular)* layer However, lymph nodes overlooked during the primary dissection from the axillary specimen but subsequently discovered by control roentgen examinations and dissected *at the* second or third trial could not as a rule be properly located in their original anatomic positions

In summary the postoperative investigations of the specimen included roentgen examination quantitative measurements of radioactivity autoradiography, and histologic examination The technique and procedures involved in these investigations have been described by HULTBORN et coll (1970)

Results

A total of 375 axillary lymph nodes from the eight patients were found and examined for Lipiodol *and* ^{198}Au As many as 322 (85 9 %) of the nodes contained radioactive tracer as well as Lipiodol The radioactive tracer alone was demonstrated in 25 lymph nodes Lipiodol alone *in* 17, and 11 nodes

Table

Distribution of injected ¹⁹⁸Au and Lipiodol (and metastases) in axillary lymph nodes (lnn) from eight patients operated on for carcinoma of the breast

Case No	Number of lymph nodes removed	Lnn containing ^{198}Au and Lipiodol	Lnn with only ^{198}Au	Lnn with only Lipiodol	Lnn without ^{198}Au and Lipiodol	Lnn with metastases
1	38	29	2	2	5	0
2	63	59	3	0	1	3
3	46	37	8	1	0	0
4	35	31	3	0	1	0
5	62	55	5	0	2	4
6	58	53	1	4	0	0
7	40	35	1	3	1	0
8	31	23	0	7	1	0
Total	375	322	23	17	11	7

the axillary region was examined roentgenographically and any lymph nodes that had been overlooked were identified and removed separately

Lymph node dissection The axillary fat with its lymph nodes was now placed, corresponding to its situation in the axilla, on a film and examined roentgenographically under more favourable conditions This detailed roentgenogram (specimen lymphadenogram) enabled the lymph nodes finally to be dissected out from the axillary fat, numbered and mapped in series for an individual still more detailed roentgen examination to evaluate the presence of Lipiodol

The remaining fat was always roentgenologically re examined to make sure that no lymph nodes had been missed The dissection was thus sometimes repeated up to three times The breast and pectoral muscles were investigated similarly and great care was taken in searching for lymph nodes on the dorsal aspect of the pectoralis major muscle, thus including interpectoral nodes After this phase was completed, all lymph nodes and axillary fat were kept for further quantitative measurements of radioactivity High activity in the remaining axillary tissue probably indicated the presence of overlooked lymph nodes, and the specimen was redissected The next step was to prepare histologic sections for direct examination and for autoradiography

A detailed orientation during the different steps of the operative procedure in six patients (see page 67) allowed an almost exact anatomic localization of most of the lymph nodes in the axillary fat as well as of those removed separately

mastectomy with meticulous lymph node dissection of the axilla There were 21 5 lymph nodes per specimen in a very thoroughly dissected group In a cleared group (Spalteholz method) there were 37 3 lymph nodes per specimen The average number in the present series was 47 axillary lymph nodes despite the fact that the age of the patients was fairly high (54 to 77 mean 62 years) It is well known that a progressive decrease in the number of lymph nodes occurs with age It therefore seems reasonable to conclude that the vast majority of the axillary lymph nodes in this series of patients were in fact removed

A detailed investigation was performed to find out why some nodes lacked either or both substances (Lipiodol and ^{198}Au) No single cause could be estab lished It is however known that inflammatory reactions acute or chronic fat in- volvement and fibrosis can interfere with the function of lymph nodes resulting in poor or absent filling with injected substances (HULTBORN et coll 1955 and HULTEN et coll 1966) Furthermore the radioactive marker retained within a node could probably cause a radiation reaction if the dose is high This might deviate the lymph flow and obstruct the entry of particles arriving subsequently particularly particles of larger dimensions, e g Lipiodol This hypothetical explanation is probably of minor importance as most lymph nodes with large amounts of tracer were also heavily loaded with Lipiodol However a radiation effect has in fact been noted in the form of slight oedema and cell depopulation around clusters of tracer substance in the nodes and this might indicate a deviation of lymph flow

The occurrence of either substance alone in occasional nodes is probably due to individual variations in lymph flow which means that there is no complete overlapping in the axilla of the flow from the arm and the breast respectively as could also be expected on biologic grounds

The distribution of the injected radioactive substance might also have been affected by the neoplasm itself Thus twenty three of twenty eight lymph nodes in which no radioactivity was demonstrated belonged to a group of four patients in whom the growth was located between the site of the injected ^{198}Au and the axilla In other words, a tumour block may have existed in these cases

The present results indicate clearly that most axillary lymph nodes serve two areas of lymphatic drainage the arm and the breast It cannot be assumed that the lymph from these areas drains to different groups of nodes within the axilla though it must be admitted that different groups of nodes may be affected primarily in the course of inflammatory or neoplastic disease

From the surgical point of view it must therefore be stressed that all nodes must be excised when the lymph nodes in the axilla are to be *removed radically* for carcinoma of the breast Separate regional groups of nodes draining the arm and the breast do not exist and elective removal is therefore impossible

contained neither ^{198}Au nor Lipiodol. Thus, 28 lymph nodes had no radioactivity and 36 lymph nodes contained no contrast medium (see Table).

Among the twenty five lymph nodes containing only the radioactive marker, four were located infraclavicularly, six in the axillary vein group and five in the central group of the axilla. Ten nodes could not be topographically identified for technical reasons.

Of the seventeen lymph nodes containing only Lipiodol, eight were located in the axillary vein group and seven in the central group. Two could not be located topographically.

Of the eleven lymph nodes containing neither radioactive substance nor Lipiodol, two were located infraclavicularly, two in the central region and one in the axillary vein group. Six nodes belonging to this category were lost for proper identification.

Two of the patients had axillary metastases, in one patient three lymph node metastases were found, in the other four. In all the lymph nodes with metastases, except one, Lipiodol as well as the tracer were present.

Discussion

The present results indicate that both Lipiodol introduced by direct lymphography of the dorsum of the hand and ^{198}Au injected into the mammary gland are distributed widely to the axillary lymph nodes, their concomitant occurrence could be demonstrated in 86 % of the nodes. The two substances occurred separately only in a small proportion of nodes and in a still smaller proportion of nodes that contained neither substance were demonstrated.

In evaluating these results, attention must be paid to whether the majority of the axillary lymph nodes were removed at operation. However, our operative procedures have always been thorough and carefully checked by repeated roentgen examinations (see Fig 3). Furthermore, a magnifying glass was used in the dissection of lymph nodes from the specimen. The tissue lymphadenogram always served as the guide for the identification of individual nodes. Overlooked lymph nodes were detected either by repeated roentgen examination or by the occurrence of radioactivity in the remaining axillary fat specimen.

The Spalteholz clearing method for identifying minute lymph nodes (cf HULTBORN 1952) seems to be less appropriate for axillary lymph nodes, since a high proportion of these exhibit fat involvement and would be made invisible by this technique.

Following mastectomy, the excised axillary lymph nodes in the operation specimen have been studied by several previous investigators by the Spalteholz method. Thus, PICKREN (1956) compared two series of specimens after radical

FROM THE DEPARTMENT OF RADIOLOGY, YALE UNIVERSITY SCHOOL OF MEDICINE
NEW HAVEN CONNECTICUT, USA

MATHEMATICAL SIMULATION OF RADIATION THERAPY OF SOLID TUMORS

I Calculations

by

JAMES J FISCHER

The enormous growth in knowledge of the response of individual mammalian cells to radiation which has followed the pioneer work of PUCK & MARCUS (1956) and HEWITT & WILSON (1959) has supplied ample material for the model builder attempting to describe in mathematical terms the radiotherapy of solid tumors Previous attempts to create such mathematical models however, have often led to results markedly different from clinical experience and have in fact even resulted in postulation that mechanisms other than direct cell kill such as immunologic responses, effects of radiation on the tumor bed and other unknown defense mechanisms must contribute substantially to tumor destruction The earlier models while useful in illustrating the individual effects of some of the more important variables, such as initial cell number and degree of oxygenation, have contained such gross simplifications that not surprisingly the calculated dose levels required for tumor control have generally been unrealistic (FOWLER 1966)

With the ready availability of modern computation facilities it has become feasible to develop and use a model which takes into account many experimentally established radiobiologic principles which are thought to be important in the

Submitted for publication 1 December 1969

SUMMARY

Eight patients with mammary carcinoma were examined by preoperative injection of ^{198}Au into the breast parenchyma and by lymphography via the lymph vessels of the hand to elucidate the topography of the lymph drainage of the breast and arm to the axillary nodes The investigation has clearly indicated that all axillary lymph nodes must be removed when axillary lymphadenectomy is included in the treatment

ZUSAMMENFASSUNG

Acht Patienten mit Brustdrusenkarzinom wurden preoperativ mittels ^{198}*Au Injektion in* das Brustparenchym und mit Lymphographie der Gefässe der Hand untersucht um die Topographie des Lymphabflusses von Brust und Arm zu den axillären Lymphknoten zu erleuchten Die Untersuchung hat deutlich gezeigt dass alle axillären Lymphknoten entfernt werden mussen wenn die Behandlung eine Lymphadenektomie einschliesst

RÉSUMÉ

Huit malades atteintes de cancer du sein ont été examinées par injection pré opératoire *de* ^{198}*Au dans le parenchyme du sein et par lymphographie des vaisseaux de la main pour* determiner la topographie du drainage lymphatique du sein et du bras dans les ganglions axillaires Cette recherche a montré clairement qu il faut enlever tous les ganglions lym *phatiques axillaires quand le traitement comporte une lymphadénectomie axillaire*

REFERENCES

HULTBORN K A Cancer of the colon and rectum Acta chir scand (1952) Suppl No 172 p 49

— and JONSSON L E The use of colloidal Au^{198} for the detection of lymph nodes in radical excision of the breast Acta radiol 43 (1955) 132

— LARSSON L G and RAGNHULT I The lymph drainage from the breast to the axillary and parasternal lymph nodes studied with the aid of colloidal Au^{198} Acta radiol 43 (1955) 52

— HULTÉN L ROOS B et coll Evaluation of regional lymph drainage from mammary gland and hand to axillary nodes Acta radiol Ther Phys Biol 9 (1970) 489

HULTÉN L AHRÉN CH and ROSENCRANTZ M Lymphangio adenography in carcinoma of the breast Comparative clinical roentgen and histologic appraisal of the method for the demonstration of lymph node metastases Acta chir scand 132 (1966) 261

KENDALL B E ARTHUR J F and PATEY D H Lymphangiography in carcinoma of the breast A comparison of clinical radiological and pathological findings in axillary lymph nodes Cancer 16 (1963) 1233

PICKREN J W Lymph node metastasis in carcinoma of the female mammary gland Roswell Park Bull 1 (1956) 79

TURNER WARWICK R T The lymphatics of the breast Brit J Surg 46 (1959) 574

FROM THE DEPARTMENT OF RADIOLOGY, YALE UNIVERSITY SCHOOL OF MEDICINE
NEW HAVEN, CONNECTICUT USA

MATHEMATICAL SIMULATION OF RADIATION THERAPY OF SOLID TUMORS

I Calculations

by

JAMES J FISCHER

The enormous growth in knowledge of the response of individual mammalian cells to radiation which has followed the pioneer work of PUCK & MARCUS (1956) and HEWITT & WILSON (1959) has supplied ample material for the model builder attempting to describe in mathematical terms the radiotherapy of solid tumors. Previous attempts to create such mathematical models, however, have often led to results markedly different from clinical experience and have in fact even resulted in postulation that mechanisms other than direct cell kill such as immunologic responses effects of radiation on the tumor bed and other unknown defense mechanisms must contribute substantially to tumor destruction The earlier models while useful in illustrating the individual effects of some of the more important variables, such as initial cell number and degree of oxygenation, have contained such gross simplifications that not surprisingly the calculated dose levels required for tumor control have generally been unrealistic (FOWLER 1966)

With the ready availability of modern computation facilities it has become feasible to develop and use a model which takes into account many experimentally established radiobiologic principles which are thought to be important in the

Submitted for publication 1 December 1969

therapy situation Factors which seemed a priori to be of significance and which have thus been incorporated into the model include the effect of hypoxia on individual cell response to radiation, cellular recovery from sublethal damage, radiation induced division delay, multiplication of viable cells during the course of therapy, persistence of sterilized cells in the tumor volume, and the possibility of re oxygenation of hypoxic cells as the total tumor volume decreases The variation in cell sensitivity throughout the mitotic cycle and the possibility of cell population synchronization have been ignored The significance of these related phenomena in radiation therapy has not been definitely established (WHITMORE & TILL 1964) and any attempt to introduce them into the complete model would be extraordinarily complicated although in fact possible With this exception, the model accounts in some way for all factors of obvious importance

Basic assumptions The basic assumption incorporated in the model are discussed in detail below

1 Cells are killed by radiation according to the well known expression

$$S = 1-(1-e^{-D/D_o})^n \quad (1)$$

where S is the probability of a cell surviving following radiation with dose D, e is a base of the natural logarithm, and n and D_o are constants called the 'hit or extrapolation number' and the 'characteristic dose respectively, which characterize any particular system This relationship may be derived from a multi target, single hit kill model or it may be considered to be a strictly empirical relationship which has been found to describe experimental observations

For our purposes a cell is considered to be dead when it is unable to reproduce indefinitely, thereby perpetuating the cell line Cells which are alive by this definition are commonly called 'clonogenic Death specifically does not imply that the cell has ceased to exist as a grossly intact, metabolizing entity

2 The probability of cure of the tumor, Pc, is the probability that no cells remain alive following treatment and is calculated from the Poisson distribution

$$P_c = e^{-s} \quad (2)$$

where s is the expected number of surviving cells

The actual program is designed to permit a more general definition of cure namely that the number of surviving cells be less than any arbitrarily specified number m The cure probability is then obtained by summing the probabilities of each number less than m actually occurring when the expected number surviving is s The result follows directly from the Poisson distribution

$$P_c = \sum_{\lambda=0}^{\lambda=m-1} \frac{e^{-s} s^{\lambda}}{\lambda!} \quad (2a)$$

Unless otherwise indicated however, the previous definition of cure in eq (2) will be used

3 For purposes of estimating radiation response the tumor is made up of two types of cells well oxygenated cells and hypoxic cells each of which will be killed according to eq (1) but each with different characteristic parameters n and D_o labeled NO and DO and NA and DA respectively

4 The fraction of the total cells present which are well oxygenated is given by $e^{-\beta N}$ where N is the total number of cells and β is a constant to be specified

$$\frac{N_{ox}}{N} = e^{-\beta N} \tag{3}$$

5 The oxygenated cells multiply with a rate constant α and the hypoxic cells do not multiply Thus the growth of the untreated tumor is described by

$$\frac{dN}{dt} = \alpha N e^{-\beta N} \tag{4}$$

Much of the uniqueness of this model is contained in assumptions (4) and (5) and their justification and implications deserve comment The tumor growth described by eq (4) is typical of patterns observed clinically When the tumor is small and smallness is determined by β and requires that $\beta N << 1$ the growth is exponential with characteristic time α As the tumor becomes larger this growth rate is attenuated by the factor $e^{-\beta N}$, however the growth rate never becomes zero and the tumor constantly increases in size

It is of interest to note the similarity of the general features of tumor growth described by this equation and those of other standard curves commonly chosen to approximate such growth The most familiar of these is the Gompertzian relationship

$$N = ae^{-be^{-ct}}$$

where a b and c are parameters and t is the time of tumor growth

The differential equation (4) can be solved to give N implicitly by

$$\ln N + \frac{BN}{1!} + \frac{(BN)^2}{2\,2!} + \frac{(BN)^3}{3\,3!} \cdots = \alpha t + c$$

This cumbersome relationship is of no particular concern since for our purposes there is no need to solve for N explicitly It is the simplicity of the differential form eq (4) which has led to its selection

The specific identification of the attenuation factor $e^{-\beta N}$ as the fraction of cells oxygenated will now be made Thus the tumor consists of a total of $Ne^{-\beta N}$ cells which are oxygenated, grow with rate constant α and respond to radiation

according to eq (1) with parameters NO and DO, and a total of $N (1-e^{\beta N})$ cells which are poorly oxygenated, do not reproduce and are killed according to eq (1) with parameters NA and DA

This identification seems a priori reasonable Certainly one of the most important factors ultimately limiting tumor growth is the availability of oxygen and necessary substrates to all of the tumor cells The influence of total cell number or tumor size on the fraction of cells so handicapped must be quite similar to its effect on radiation sensitivity through local hypoxia

It should be noted that the growth constant, α, describes the rate of increase of the well oxygenated cells as a whole but implies no detailed information concerning the fraction of cells within this group that are actually dividing or their generation times The careful reader will discover subsequently, as cells are shifted from one group to another, that inaccuracies would be introduced if any cells in the well oxygenated group did in fact remain in a non dividing state for prolonged periods of time

6 As previously stated, cells which have been killed in the sense that they no longer can propagate may still exist in a grossly intact form Since these cells will contribute to the bulk of the tumor, any calculation of the fraction of cells that are well oxygenated, using eq (3), must include both living and dead cells in the total cell number

7 Dead cells will cease to exist only when they attempt to divide There is considerable evidence to suggest that most cells, with the possible exception of lymphocytes, when exposed to radiation at the dose levels used in therapy do not undergo intermitotic metabolic death In fact there is the possibility that cells which are dead by our original definition may divide several times producing metabolically viable daughter cells, all of which will ultimately disintegrate while attempting to reproduce This possibility of a transient increase in the number of dead cells will be ignored in the model, and it will be assumed that each dead cell disintegrates at its first attempted division The further assumption will be made that the dead cells attempt division at the same rate as the viable cells, i e α if they are oxygenated and not at all if they are anoxic

8 Provision is made to account for radiation induced mitotic delay The delay time, Δt is assumed to be linearly related to the dose

$$\Delta t = \gamma D \tag{5}$$

where γ is a parameter to be specified This form is in rough agreement with experimental results with isolated cells (LEA 1956, DOIDA & OKADA 1969) In the fractionated treatment model the reproduction of oxygenated living cells and the disintegration of oxygenated dead cells begins only after this delay period has elapsed

Table

Flow sheet

Step	Population				Calculations
	Live Ox	Dead Ox	Live Anox	Dead Anox	
Initial	N_1	N_2	N_3	N_4	$R = \dfrac{N_1 + N_2}{N_3 + N_4} = \dfrac{e^{-\beta N}}{1 - e^{-\beta N}}$
I After irradiation	N_1^{I}	$N_2^{I} = (N_1 + N_2 - N_1^{I})$	N_3^{I}	$N_4^{I} = (N_3 + N_4 - N_3^{I})$	$N_1^{I} = N_1[1-(1-e^{-D/DO})^{NO}]$ $N_3^{I} = N_3[1-(1-e^{-D/DA})^{NA}]$
II After reproduction	N_1^{II}	N_2^{II}	$N_3^{II} = N_3^{I}$	$N_4^{II} = N_4^{I}$	$\Delta t = D \quad \tau = t - \Delta t$ $N_1^{II} = N_1^{I} e^{\alpha\tau} \quad N_2^{II} = N_2^{I} e^{\ldots\tau}$
III After reoxygenation	N_1^{III}	N_2^{III}	N_3^{III}	N_4^{III}	$N^{III} = N_1^{II} + N_2^{II} + N_3^{II} + N_4^{II}$ $R^{III} = \dfrac{e^{-\beta N^{III}}}{1 - e^{-\beta N^{III}}}$ N_i^{III} s from Appendix

Mathematical form of the model A flow sheet describing the sequence of calculations is given in the Table For a fractionated treatment regimen the sample set of calculations is applied iteratively for each treatment always starting with the appropriate initial cell populations taken from the preceding cycle Four cell populations are followed throughout and those are designated consistently by the subscript of N such that $1 =$ living oxygenated $2 =$ *dead* oxygenated $3 =$ living anoxic and $4 =$ dead anoxic

The calculation is done in three steps radiation kill reproduction, and reoxygenation in that order and the cell number in any of the population groups described above is designated with respect to the calculation step completed by the superscripts I II and III Thus N_3^{II} would designate the population of live anoxic cells following the reproduction calculation

The first line of the Table gives the initial population levels which as previously noted will come from the preceding calculation cycle For the initial treatment only $N_2 = N_4 = 0$ i e there are no dead cells prior to treatment The fraction oxygenated is determined as indicated in the right hand column which is derived directly from assumption (4)

In step I living cells N_1 and N_3 are killed by the radiation in accordance with assumption (1) using the appropriate constants depending upon their state of oxygenation The newly killed cells are then added to the populations of dead cells as indicated without changing the oxygenation of the individual cells

Step II calculates the cell populations after reproduction has occurred through the period of time between treatments The actual time period is reduced by the mitotic delay time, Δt, before the calculation is carried out In agreement with assumptions (5) and (7), only the oxygenated cells divide, and as the oxygenated dead cells attempt division they disappear from the cell pool

Following reproduction and just prior to the next irradiation, a provision for re oxygenation is made The new total cell number, N^{III} is determined and is used to calculate a new ratio of oxygenated to anoxic cells A shifting of cells among the four population groups is carried out to establish this new ratio, with the obvious restriction that live and dead cells retain that identity as their state of oxygenation changes It is further assumed that the oxygenation procedure cannot distinguish between living and dead cells in selecting which cells are to change their state of oxygenation The equations necessary for calculating the new population levels are derived in the appendix using these assumptions This entire cycle is then repeated for the next radiation treatment It is assumed that the treatments are separated sufficiently in time, usually at least twenty four hours so that individual cell recovery from sub lethal damage is complete (ELKIND & SUTTON 1960), and cell kill is once again described by eq (1)

Computer program A computer program to carry out the above calculations has been written in the Fortran IV language and is currently being used on the Yale Computer Center IBM 360/50 time sharing system Input and read out can be accomplished at a remote terminal located in the Department of Radiology The program includes detailed prompting' to guide even the most inexperienced operator, and it has thus been possible to teach radiation therapy residents to use it with less than one hour of instruction

Input data required includes the total number of cells initially present in the tumor and the constants alpha, beta, gamma, *NO, NA, DO,* and *DA* previously described In addition, the operator must choose a treatment regimen which may consist of any arbitrary number and pattern of treatment days per week and any daily dose level After each treatment the cure probability is calculated, and the program continues to run until some arbitrary level, usually 95 %, or some specified total number of treatments, usually 50, has been reached When this computation has been completed, the operator may ask for the cure probabilities following any particular daily treatment based on any alternative definition of cures as described in eq (2a)

After initially introducing the necessary tumor parameters enumerated above, the operator has the option of requesting that the computer automatically carry out the simulated treatments at a wide range of daily treatment doses, thus accumulating all the data necessary to plot a Strandqvist type time dose curve

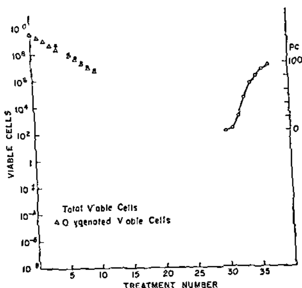


Fig 1 Cure probability as a function of dose

When the most detailed data output is requested the number of cells in each of the four categories is given for each of the three calculation steps for every radiation dose In addition after each treatment the total number of cells the proportion alive the proportion oxygenated and the cure probability are calculated Various optional abbreviated output formats are available for special applications and for teaching purposes

A typical calculation for a thirty treatment course requires 1 to 2 seconds of computation time The total cost depends mainly on the output form desired and may range from less than one to several dollars at current rates

Sample calculation A sample calculation is presented here for treatment of a tumor with the following characteristics $N = 10^{10}$, alpha $= 0\ 004$/hours beta $= 10^{10}$ gamma $= 0\ 005$ hours/rad $VO = 4$, $DO = 100$ rad $NA = 1$, $DA = 250$ rad The values given are realistic The total cell number corresponds to a tumor mass several centimeters in diameter The inherent doubling time is one week The value of beta has been chosen to give initially an unusually high proportion of anoxic cells 63 % This was done deliberately to demonstrate the importance of re-oxygenation The value of gamma results in a mitotic delay of 1 hour for a dose of 200 rad in agreement with experimental observations

The tumor is treated using a five day treatment week and a daily dose of 200 rad The cure probability as a function of dose is plotted in Fig 1 It becomes

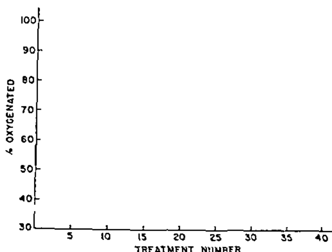


Fig 2 Per cent of oxygenated cells can be seen to increase with the number of radiation treatments given

finite at approximately 6 000 rad and reaches 95 % at 7 400 rad, in agreement with clinical experience for epithelial tumors of this size. The total number of viable cells and the number of oxygenated viable cells throughout the treatment course are also shown in Fig 1 By the tenth treatment these numbers are approximately the same, demonstrating the effects of the re oxygenation mechanism This is shown more explicitly in Fig 2 where the percentage oxygenated cells can be seen to increase during the treatment This must be contrasted with the results of static models in which the population of oxygenated cells is depleted initially, because of their greater sensitivity, and later doses exert their effect on a population of cells which essentially is entirely hypoxic (POWERS & TOLMACH 1963)

The decrease in total cell number and thus in the overall tumor size is shown in Fig 3 This change is less than two orders of magnitude, much less than that seen in Fig 1 for the viable cells alone, and the tumor could probably still be detected by physical examination at the completion of the treatment

Discussion

The model described was designed to be as simple as possible while still accounting in some way for the radiobiologic factors thought to be most important in radiation therapy The tumor is characterized by eight parameters values of which can be estimated from experimental and clinical observations The results of calculations using a variety of reasonable values for these parameters have been in surprising agreement with clinical experience

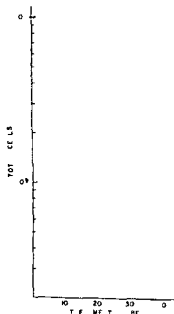


Fig 3 The total cell number and thus the o e all tumor size de rea es as a f nction of the num ber of radiation treatments given

The sample tumor system described in detail illustrated a number of characteristic findings the dose response curve for cure was realistic for a tumor of this size the slow decrea e in total cell mass agrees with clinical observations of response to treatment in slow ly growing tumors and the importance of re oxygenation of hypoxic tumor cells was dem onstrated Subsequent publications will detail the effects of systematically varying the tumor parameters and the effects of various less commonly used treatment doses and schedules

In order to achieve the desired simplicity in the model a number of assumptions were necessary These were described in explicit detail so that the reader might evaluate them in terms both of limiting his confidence, in the applicability of the calculated results and of possibly improving the model by accounting for additional radiobiologic factors It is not possible to review here the vast experimental evidence which collectively supports the cur rent theories concerning the nature of the radiation therapy of tumors, however a fa miliarity with any of the several excellent recent reviews of this subject will provide an appropriate perspective (ANDREWS 1968 FOWLER 1966 WHITMORE & TILL 1964) Many of the assumptions have been used commonly in the past and will therefore meet with little objection

When deciding upon new features to be incorporated into the model it is necessary to balance the possible improvement against the resulting increased complication For example it would be quite simple to use any desired formula for cell kill including the so called multi hit multi target expressions which lead to constantly increasing slopes of the survival do e curves However in view of the uncertainties in the values of the necessary parameters it seems unlikely that any significant improvement would be achieved for the dosage schemes being u ed in therapy Likewise a more complicated expres ion for division delay while not difficult to introduce into the program would hardly alter the calculated results

In contrast it would be quite difficult to account for changes in cellular radiation re ponse throughout the mitotic cycle This would require definition of

a number of new subdivisions of the total cell population with varying sensitivi and establishment of a pattern for shifting individual cells among these sul populations Despite considerable interest in this phenomenon it has not bee definitely shown that it is of importance under clinical conditions (TERASMIA TOLMACH)

One promising area for improvement is the description of the kinetics of ce reproduction It should be possible to account for the presence of cells with variety of division rates It may also be important, especially since re oxygenatio has been made dependent on total cell number, to account for the fact that kille cells may go on to produce a limited number of daughter cells

There can now be little doubt that re oxygenation of hypoxic cells durin radiation therapy does occur and is of considerable importance (VAN PUTTEN KALLMAN 1968, VAN PUTTEN 1968) Several possible re oxygenation mechanism have been proposed One of the simplest, and that which has been used her considers that the proportion of cells which are hypoxic is related only to th total number of cells present Such a situation might arise if the tumor cel multiplied too rapidly for the development of an adequate vasculature It woul be assumed that the state of oxygenation of any given cell would depend on i location in a specific region of the tumor and would not vary in time unless th total cell number were changed Re oxygenation of hypoxic cells would occu only as a result of a decrease in tumor size, and then only in the manner describe in the appendix

A second mechanism would exist if the oxygen tension at any point in th tumor were fluctuating in time This might happen in such a way that at an instant in time a certain fixed fraction of the cells might be hypoxic, but with n individual cell constantly hypoxic For such a situation there is an obviou rationale for fractionated radiation therapy

A third possible mechanism for re oxygenation exists in the development i time of the necessary increased vasculature While it may seem superficially tha this could occur spontaneously, without the aid of the therapist, in actual fac this is unlikely It is most probably due simply to the disparity in the rates o multiplication of the tumor cells and the development of vasculature that hypoxi cells do exist, and all experience seems to indicate that even larger proportions o cells are hypoxic as the tumor grows Nevertheless, if some factor such as radiation treatment can slow or stop tumor growth, this mechanism provides for possible re oxygenation which is time dependent and not necessarily cell number de pendent

One might refer to these three mechanisms respectively as cell number depen dent' and 'non secular time dependent' and secular time dependent' re

occur to some extent The demonstration of their relative importance is an important experimental problem and the incorporation of such information into a model will represent a substantial improvement in the theory of radiation therapy

Appendix

Re-oxygenation equations The following four independent equations are used to solve for the new population levels

$$N^{III} = N_1^{III}+N_2^{III}+N_3^{III}+N_4^{III} = N_1^{II}+N_2^{II}+N_3^{II}+N_4^{II} \qquad (A\ 1)$$

this condition arises from the conservation of the total cell number

$$R^{III} = \frac{e^{-\beta V^{III}}}{1-e^{-\beta V^{III}}} = \frac{N_1^{III}+N_2^{III}}{N_3^{III}+N_4^{III}} \qquad (A\ 2)$$

determining the new ratio of oxygenated to anoxic cells

$$N_1^{III}+N_3^{III} = N_1^{II}+N_4^{II} \qquad (A\ 3)$$

this equation insures conservation of the number of living cells and with (A 1) likewise conserves the number of dead cells

$$\frac{N_3^{III}}{N_4^{III}} = \frac{N_3^{II}}{N_4^{II}} \quad \text{for } R^{III} > R^{II}$$

$$\frac{N_1^{III}}{N_2^{III}} = \frac{N_1^{II}}{N_2^{II}} \quad \text{for } R^{III} < R^{II} \qquad (A\ 4)$$

where

$$R^{II} = \frac{N_1^{II}+N_2^{II}}{N_3^{II}+N_4^{II}}$$

This last set of equations (A 4) provides that when a net shift must occur from the anoxic to the oxygenated groups the proportion of the anoxic cells which are alive will be the same before and after the shift and when the shift must occur in the other direction increasing the anoxic number the proportion of the oxygenated cells alive is conserved These results follow from the a priori reasonable assumption that the act of changing the state of oxygenation cannot distinguish between living and dead cells

The simultaneous equations are easily solved to give the explicit expressions for the new populations

For $R^{III} > R^{II}$

$$N_1^{III} = N_1^{II} + N_3^{II} - \frac{N_3^{II}}{N_4^{II}} L$$

$$N_2^{III} = N_2^{II} + N_4^{II} - L \qquad (A\ 5)$$

$$N_3^{III} = \frac{N_3^{II}}{N_4^{II}} L$$

$$N_4^{III} = L$$

where

$$I = \frac{\mathcal{N}^{III}}{(1+R^{III})\left(1+\frac{\mathcal{N}_3^{II}}{\mathcal{N}_4^{II}}\right)}$$

For $R^{III} < R^{II}$

$$\begin{aligned}
\mathcal{N}_1^{III} &= \frac{\mathcal{N}_1^{II}}{\mathcal{N}^{II}} M \\
\mathcal{N}_2^{III} &= M \\
\mathcal{N}_3^{III} &= \mathcal{N}_1^{II} + \mathcal{N}_3^{II} - \frac{\mathcal{N}_1^{II}}{\mathcal{N}^{II}} M \\
\mathcal{N}_4^{III} &= \mathcal{N}^{II} + \mathcal{N}_4^{II} - M
\end{aligned} \qquad \text{(A 6)}$$

where

$$M = \frac{R^{III}\mathcal{N}^{III}}{(1+R^{III})\left(1+\frac{\mathcal{N}_1^{II}}{\mathcal{N}^{II}}\right)}$$

Acknowledgements

I would like to thank D B Fischer of the Yale Computer Center for her interest in this project and for writing a most elegant program to carry out the necessary computations M M Kligerman for valuable discussions and suggestions for improvement and M C Jost who helped with the preparation of the data This work was supported by the United States Public Health Service grant No CA 06519

SUMMARY

A mathematical model has been developed to simulate the treatment of solid tumors with radiation therapy It is sufficiently detailed to take into account differences in sensitivity of hypoxic and well oxygenated cells radiation induced mitotic delay reproduction of viable cells between treatments delayed dissolution of sterilized cells and re oxygenation of hypoxic cells as the tumor decreases in size Any desired treatment regimen may be specified The results obtained in using this model agree exceptionally well with known clinical and experimental data A sample calculation is presented in detail

ZUSAMMENFASSUNG

Ein mathematisches Modell wurde entwickelt um die Veränderungen solider Tumoren bei der Behandlung durch die Strahlentherapie zu simulieren Dieses ist hinreichend detailliert um Unterschiede in der Empfindlichkeit von hypoxischen und gut Sauerstoff versorgten Zellen die strahleninduzierte Verzögerung der Mitosen die Vermehrung viabler Zellen zwischen den Behandlungen die verzögerte Zerstörung sterilisierter Zellen und die Reoxygenierung hypoxischer Zellen mit sinkender Tumorgrösse zu berücksichtigen Jedes gewünschte Behandlungsregime kann im einzelnen angegeben werden Die bei der Ver

wendung dieses Modells erhaltenen Ergebnisse stimmen aus erordentlich gut mit den bekann ten klinischen und experimentellen Daten uberein Eine Probe Berechnung wird im ein zelnen dargestellt

RÉSUMÉ

L auteur a mis au point un modele mathematique pour simuler le traitement de tumeurs solides par radiotherapie Ce modele est assez detaille pour tenir compte des differences de sensibilite des cellules hypoxiques et des cellules bien oxygenees du retard de mitose induit par les radiations de la reproduction des cellules viables entre les traitements de la dissolution retardee des cellules sterilisees et de la reoxygenetion des cellules hypoxiques a mesure que le volume de la tumeur diminue On peut definir tous les types voulus de traitement Les résultats obtenus au moyen de ce modele concordent exceptionnellement bien avec les donnees connues de la clinique et de l experimentation Un exemple de calcul est presente en detail.

REFERENCES

ANDREWS J R The radiobiology of human cancer radiotherapy W B Saunders Philadelphia 1968

DOIDA Y and OKADA S Radiation induced mitotic delay in cultured mammalian cells Radiat Res 38 (1969) 513

ELKIND M M and SUTTON H Radiation response of mammalian cells grown in culture I Repair of X ray damage in Chinese hamster cells Radiat Res 13 (1960) 556

FOWLER J F Radiation biology as applied to radiotherapy *In* Current topics in radiation research Edited by M Ebert and A Howard Vol 2 North Holland Publ Co Amsterdam 1966

HEWITT H B and WILSON D W A survival curve for mammalian cells irradiated in vivo Nature 183 (1959) 1060

LAJTHA L G and OLIVER R Cell population kinetics following different regimes of irradiation Brit J Radiol 35 (1962) 131

LEA D E Actions of radiations on living cells 2nd edition Cambridge University Press Cambridge 1962

POWERS W E and TOLMACH L J A multicomponent X ray survival curve for mouse lymphosarcoma cells irradiated in vivo Nature 197 (1963) 710

PUCK T T and MARCUS P I Action of X rays on mammalian cells J exp Med 53 (1956) 653

TERASIMA T and TOLMACH L J Variations in several responses of HeLa cells to X irradiation during the division cycle Biophys J 3 (1963) 11

VAN PUTTEN L M Tumour reoxygenation during fractionated radiotherapy studies with a transplantable mouse osteosarcoma Europ J Cancer 4 (1968) 173

— and KALLMAN R F Oxygenation status of a transplantable tumor during fractionated radiation therapy J nat Cancer Inst 40 (1968) 441

WHITMORE G F and TILL J E Quantitation of cellular radiobiological responses Ann Rev nucl Sci 14 (1964) 347

FROM THE CHROMOSOME LABORATORY, INSTITUTE OF PATHOLOGY, KOMMUNEHOSPITALET, COPENHAGEN, DENMARK, RADIUMHEMMET, AND STATENS STRALSKYDDSINSTITUT, KAROLINSKA SJUKHUSET, STOCKHOLM, SWEDEN

PRIMARY POLYCYTHAEMIA

Correlations between the histologic appearances and the chromosome pattern of the bone marrow cells during the disease

by

J VISFELDT, S FRANZEN and B TRIBUKAIT

Previous investigations into the chromosomal pattern of bone marrow cells in a number of non malignant haematologic disorders disclosed aberrations in several patients with primary polycythaemia who had been treated with ^{32}P over long periods (VISFELDT et coll 1970)

The authors have pursued these investigations further with the particular *object of elucidating the conditions at various stages of the disease* The aim of the present research was as follows a) Assessment of the value of chromosome analyses for the diagnosis of various stages of primary polycythaemia b) Comparison of the types of chromosome aberrations at various stages c) Comparison between aberrations in primary polycythaemia, acute leukaemia and radiation induced chromosome abnormalities

Material for the customary histologic and cytologic investigations together with bone marrow for chromosome analyses, were aspirated and the results obtained by the various methods of examination were compared

Submitted for publication 18 February 1970

Material and methods The patients were uniform in that they were from one hospital and had been evaluated clinically and treated by one of the authors (S F) They were selected because the object was to have four clinical groups represented untreated patients treated without bone marrow fibrosis treated with bone marrow fibrosis and treated patients in whom incipient transition into a leukaemic phase was possible A bone marrow sample from each patient was aspirated for chromosome investigations and for customary histologic and cytologic examination and at the same time peripheral blood was obtained for chromosome investigation assessment of the haematologic condition and general cytologic examination The samples for chromosome investigation were then transferred to the chromosome laboratory where they were received not later than four hours after being drawn The analyses were carried out by one of the authors (J V), who had no previous knowledge of the clinical data

The bone marrow specimens for chromosome analyses were prepared by a modification of the direct method of TJIO & WHANG (1962) The peripheral blood was examined after 48 hours culture and in other respects by the method of MOORHEAD et coll (1960) Only occasionally was material for chromosome analyses aspirated more than once from the same patient

The individual cells were usually analysed by two observers, only a small number of cells were photographed

Results

The 25 patients are classified as follows 4 untreated 9 treated without bone marrow fibrosis 5 treated with bone marrow fibrosis and 7 treated patients in whom incipient transition into a leukaemic phase was possible (Table 1) The history the results of the bone marrow investigation and the haematology were taken into account at the original diagnosis of polycythaemia The more important haematologic data on admission are given in Table 1 Furtermore, the blood status and routine cytologic and histologic bone marrow examinations at the time of chromosome analyses are stated together with the fate of the disease

The results of the chromosome analyses are presented separately in Table 2 Only high quality mitosis have been analysed the aim being to take 50 cells from each sample in which no clone formation was demonstrated and 100 cells when a clone was evident The table indicates that the desired numbers were not always obtained Both a bone marrow sample and one of the peripheral blood for chromosome investigation were obtained each time from all patients However suitable slides from the peripheral blood cultures were often difficult to obtain A lower number of blood samples than of bone marrow specimens

Table 1

Haematologic and clinical data

Patient No	Sex and age (years) at onset	Haematologic data on admission				Therapy	Length of history	Main clinical signs
		Hb	PCV	WBC	Platelets			
Untreated patients								
1	♀ 74	15 2	55	13	800		0 year	Fibrillation
2	♂ 69	16 2	64	17	900		2 years	Haematomas
3	♂ 22	15 7	54	8	670		3 years	Amputationis digiti sequelae
4	♂ 41	18 5	63	10	310		5 years	Itching ruddy complexion
Treated patients without myelofibrosis								
5	♀ 70	21 0	73	21	280	1961—69 ³²P 11 times (5—7 mCi) total 67 mCi	9 years	
6	♂ 50	21 4	68	7 2	284	1961—67 ³²P 4 times (6—8 mCi) total 30 mCi	10 years	Ruddy complexion
7	♂ 44	19 4	62	14	400	1965—69 Myleran 4—1 mg/day	11 years	Pale
8	♂ 41	19 5	66	28	855	1959—68 ³²P 9 times (6—8 mCi) total 60 mCi Myleran 1966 1968	12 years	
9	♂ 60	24 0	71	9 4	244	1957—67 ³²P 6 times (5—7 mCi) total 34 mCi	13 years	Ruddy complexion
10	♂ 59	16 6	59	10	640	1956—68 ³²P 6 times (5—7 mCi) total 38 mCi	14 years	

Table 1 *(cont.)*

Haematologic data at chromosome analysis					Histology and cytology of bone marrow	Fate of disease following chromosome analysis
Hb	PCV	WBC	Platelets	Abnormal cells in blood		
15 ?	55	13	800	0	Few fat cells hyperplasia as in primary polycythaemia no fibrosis	
16 2	64	17	900	0	No fat cells hyperplasia as in primary polycythaemia no fibrosis	
15 7	54	8	670	0	No fat cells hyperplasia as in primary polycythaemia no fibrosis	Died after 207 days of coronary thrombosis
18 5	63	10	310	0	No fat cells hyperplasia as in primary polycythaemia no fibrosis	
14 1	57	14	320	0	*Majority of fragments of normal* structure slight increase of thrombocytopoiesis no fibrosis	
16 2	63	17 4	230	0	Very few fat cells marked hyperplasia as in primary polycythaemia no fibrosis	
8 9	27	2 5	90	0	Fat cells reduced marked hyperplasia of erythropoietic series with many degenerative changes many plasma cells no fibrosis	
13 7	49	12	270	0	Normal fat content normal structure slight increase in thrombocytopoiesis no fibrosis	
18 5	64	9 8	270	0	Fat cells reduced hyperplasia of haematopoiesis particularly of thrombocytopoiesis no fibrosis	
13 3	44	6 ?	440	0	Some particles only fatty tissue others normally structured obvious increase in thrombocytopoiesis no fibrosis	

Table 1 (*cont*)

Patient No	Sex and age (years) at onset	Haematologic data on admission				Therapy	Length of history	Main clinical signs
		Hb	PCV	WBC	Platelets			
11	♀ 50	17 3	?	10 4	264	1950—68 ^{32}P 6 times (5 mCi) total 30 mCi	19 years	Multiple thromboses
12	♂ 40	15 5	59	8	800	1958—68 ^{32}P 9 times (5—7 mCi) *total 54 mCi*	19 years	Ruddy complexion
13	♀ 44	16 2	56	6 3	510	1940—68 ^{32}P ? whole body irradiation 1968 7 mCi ^{32}P	29 years	Pale
Treated patients with myelofibrosis								
14	♂ 69	7 0	*19*	*23*	*265*	*1966* spleen irradiation *1966—67* Myleran	*3* years	Marked splenomegalia
15	♀ 68	24 0	77	13	480	1961—67 ^{32}P 7 times (5 mCi) total 35 mCi	10 years	
16	♀ 53	15 6	50	11	1 900	1963—64 ^{32}P 3 times (4—6 mCi) total 16 mCi	12 years	Spleen just palpable
17	♂ 34	9 5	32	19 4	195	1968—69 Myleran	17 years	Marked splenomegalia
18	♀ 62	16 4	54	9 3	400	19??—1958 ^{32}P? *1958—69 ^{32}P 8* times (5 mCi) *total 40 mCi*	19 years	Splenomegalia
Treated patients with possible leukaemia								
19	♂ 61	15 7	53	13	335	1967 ^{32}P twice (7 mCi) total 14 mCi 1965—68 Myleran	5 years	Pale poor appearance

Table 1 *(cont)*

Haematologic data at chromosome analysis					Histology and cytology of bone marrow	Fate of disease following chromosome analysis
Hb	PCV	WBC	Platelets	Abnormal cells in blood		
8 9	44	24	270	0	Fat cells reduced hyperplasia as in primary polycythaemia no fibrosis	
15 5	51	4 9	315	0	Fat cells reduced slight increase in erythropoiesis and thrombocytopoiesis no fibrosis	
10 0	39	6 7	315	0	Some fat cells marked hyperplas a as in p imary polycythaemia no fibrosis typical myeloma cells in small clusters	
7 8	?6	19	180	5 stem cells numerous erythroblasts	No fat cells hyperplasia as in primary polycythaem a numerous polymorphic megakaryocytes slight diffuse fibros s	
9 8	33	8 5	215	0	Very few fat cells areas of hyperplasia as in pr mary polycythaemia marked diffuse and patchy fibrosis	
9 5	34	6 6	220	Very few erythroblasts and myelocytes	No fat cells hyperplas a as in pr mary polycythaemia numerous polymorphic megakaryocytes marked fibrosis	
9 5	32	19 4	195	5 stem cells many erythroblasts	No fat cells marked hyperplasia as in primary polycythaemia numerous hyperplastic megakaryocytes d ffuse fibros s	
15 5	5	6	315	0	Some fat cells hyperplas a as in primary polycythaemia d ffuse fibrosis in some areas	
9 8	33	11	160	12 stem cells many erythr blasts	No fat cells hyperplasia predominantly in granulocytic series sl ght increase of stem cells degenerative changes in erythropo etic series no fibrosis	Died after 169 days of acute leukaemia

Table 1 *(cont.)*

Patient No.	Sex and age (years) at onset	Haematologic data on admission				Therapy	Length of history	Main clinical signs
		Hb	PCV	WBC	Platelets			
20	♂ 56	16.2	61	8	440	1963—68 ^{32}P 5 times (7 mCi) total 35 mCi	6 years	Pale, poor appearance, spleen just palpable
21	♀ 76	16.4	67	17	830	1962—69 ^{32}P 7 times (6 mCi) total 42 mCi	7 years	
22	♂ 71	16.5	53	10	320	1961—68 ^{32}P 9 times (6 mCi) total 54 mCi	9 years	Pale, poor appearance
23	♀ 64	18.5	65	23	545	1959—68 ^{32}P 4 times (5 mCi) total 20 mCi	20 years	Pale, spleen just palpable
24	♀ 42	16.5	60	12	480	1955—67 ^{131}I 7 times (4—7 mCi) total 35 mCi	22 years	
25	♀ 50	15.5	53	9	500	1956—66 ^{32}P 3 times (6—7 mCi) total 19 mCi	27 years	Pale, poor appearance

Hb: g/100 ml. PCV: per cent. WBC: thousands/mm³. Platelets: thousands/mm³.

are listed in the table. These problems resulted from several factors. It is often difficult to separate the leukocyte containing plasma. The relatively high number of neutrophils in the blood in primary polycythaemia and the tendency to development of lymphopenia after irradiation may also contribute to the occurrence of poor growth. Almost 40 per cent of the blood cultures on the whole must be regarded as failures. Similar problems seem to arise in other laboratories when working with blood from patients with primary polycythaemia; MacDiarmid (1965) reported a failure rate of 40 per cent.

Table 1 *(cont.)*

Haematologic data at chromosome analysis					Histology and cytology of bone marrow	Fate of disease following chromosome analysis
Hb	PCV	WBC	Platelets	Abnormal cells in blood		
9 5	29	5	135	Very few myelocytes	Very few fat cells hyperplasia predominantly in granulocytic series more than 50 % stem cells slight diffuse fibrosis	Died after 118 days of acute leukaemia
15 9	57	25	100	54 stem cells	Very few cells 70 stem cells few megakaryocytes no fibrosis	Died after 11 days of acute leukaemia
8 6	?8	4	340	2 promyelocytes	Fat cells reduced predominance of granulocytic series a number of pathologic stem cells rather numerous hypoplastic immature megakaryocytes slight diffuse fibrosis	Died after 58 days of pneumonia
9 8	33	2?	70	70 stem cells many erythroblasts	Some fat cells about 90 stem cells no fibrosis	Died after 30 days of acute leukaemia
11 8	4?	30	210	15 stem cells many erythroblasts	No fat cells moderate number of stem cells but still elements of normal haematopoiesis marked fibrosis	Anemia thrombocytopenia
10 2	27	22	?30	3 stem cells very few erythroblasts	Some fat cells hyperplasia predominantly in granulocytic series rather numerous stem cells degenerative changes in granulocytopoetic series plenty of megakaryocytes often immature hypoplastic forms no fibrosis	Died after 313 days of acute leukaemia

The structural chromosome aberrations are according to the *general principles of radiation induced chromosome abnormalities* classified as stable or *unstable aberrations* The unstable aberrations which, as expected occur mainly *in the peripheral blood* were dicentrics ring chromosomes and acentric fragments No tricentrics were detected Because chromatid aberrations do not present any significant increase they were not included

Clone formations were recorded in bone marrow specimens from 12 patients

Table 2

Chromosome analyses

Patient No	Sample	Total analysed cells	Cells with aberrations	Clone	Abnormality*	Tentative explanation of aberrations
Untreated patients						
1	K	50	0			
2	K	30	0			
3	K	50	0			
	B	50	0			
4	K	32	9 % stable			
Treated patients without myelofibrosis						
5	K	100	0			
	B	20	15 % stable 25 % unstable			
6	K	53	87 % stable as clone j	j	46, XX, F?—	Deletion of an F group chromosome
7	K	50	0			
8	K	34	0			
9	K	100	58 % stable as clone 1	1	46, XX, D+ B+ C— C—	Translocation between two C group chromosomes
	B	14	0			
10	K	12	0			
	B	38	18 % stable 13 % unstable			
11	K	21	0			
	B	13	3 cells with stable 3 cells with unstable			
12	K	75	35 % with 47 chromosomes clone f	f	47, XX, C+	Trisomy C
	B	23	13 % stable 9 % unstable			
13	K	100	91 % stable as clone i	i	46, XX, 2+ C—	Translocation to a C group chromosome

Table 2 *(cont.)*

Patient No	Sample	Total analysed cells	Cells with aberrations	Clone	Abnormality*	Tentative explanation of aberrations
Treated patients with myelofibrosis						
14	K	79	100 stable as clone k	k	46 XY Dq—	Deletion of a D group chromosome
	B	45	15 unstable 4 stable 1 cell as clone k			
15	K	12	7? stable 58 % as clone h	h	46 XX C— D+ Dq— F?—	Deletion of C D and F chromosomes
	B	78	9 stable 1 cell as clone h 4 % unstable			
16	K	26	73 stable 61 as clone g	g	46 XX F?—	Deletion of an F group chromosome
	B	50	2 unstable			
17	K	13	0			
	B	6	0			
18	K	51	38 stable 32 as clone e	e	46 XX F?—	Deletion of an F group chromosome
Treated patients with possible leukaemia						
19	K	50	6 % stable			
	B	77	5 stable 14 unstable			
20	K	60	73 stable as clone b	b	46 XY F?—	Deletion of an F group chromosome
	B	3?	0			
	K	28	100 stable as clone b	b		
1	K	23	87 stable 83 as clone d	d	46 XX 2— 3+ Bq+	Deletion of chromosome No 2 translocation to a B group chromosome
2?	K	51	6? stable 56 as clone a	a	46 XY B— 16+	Deletion of a B-group chromosome
	B	?0	15 unstable			

Table 2 *(cont)*

Patient No	Sample	Total analysed cells	Cells with aberrations	Clone	Abnormality*	Tentative explanation of aberrations
23	K	18	0			
24	K	49	*94 % stable as clone c*	c	46 XX 1?+ B— C— C— 16+ 16+ 16+	Deletion of one B and two C chromosomes translocation to chromosome No 1
	B	100	8 % unstable 10 % *stable 4 % as clone c*			
25	K	50	2 % stable			
	B	8	0			

K bone marrow B peripheral blood * according to the Chicago Conference 1966

According to the definition of a clone, at least three cells must present characteristic and identical chromosome aberrations and these cells must possess no other chromosomal abnormalities All the 12 clones comprised many cells and amounted to 32 to 100 per cent of the cells analysed in the various bone marrow specimens

One clone, clone f, is fundamentally different from the remainder, its karyotype containing 47 chromosomes with an extra chromosome in the C group The remaining 11 clones had 46 chromosomes Table 2 presents the chromosomal pattern of the clones as recorded during the analyses, with the nomenclature applied as suggested by the CHICAGO CONFERENCE (1966) It should however be pointed out that this description is of limited value without the quantitative extent of the aberrations A tentative explanation of the morphologic changes is offered in the last column of the table, a quantitative assessment again cannot be expressed

The question as to whether the karyotypes can be presumed to be balanced or not is more important than the morphologic descriptions of the chromosome aberrations An attempt has been made to assess this factor, but the present *methodology of analysis has failed to answer this important question*

It appears that the clones present were recorded in patients who had been treated for polycythaemia over prolonged periods of time No fundamental difference between the type of the clones in the various groups of patients has been recorded A possible correlation between clone formations and the stages of the disease will be discussed

Discussion

The literature contains several reports on the chromosome investigation of bone marrow in primary polycythaemia some of which will be surveyed The results vary greatly which to some extent may depend on the stage of disease at which the examinations were performed Some authors failed to find clone formations in groups of patients of such magnitude that the present authors would have expected clones to be found (BRAUNSTEINER et coll 1964 KIOSSOGLOU et coll 1966 NAGY & YURCUTIS 1968 JENSEN 1968)

Other authors have described the detection of clones SOLARI et coll (1962) reported on a patient with myeloid metaplasia following primary polycythaemia of long duration in whom diploid bone marrow cells presented a karyotype in which one C group chromosome was replaced by a small acrocentric chromosome LEVAN et coll (1964) described a patient with primary polycythaemia in whom blood culture preparation contained various clones with chromosome number ranging from 47 to 49 ENGEL et coll (1968) described the chromosome analysis of blood cultures with Phytohaemagglutinin in a patient with myelosclerosis The chromosomal pattern corresponded completely to that found by the present writers in clone K with a Dq chromosome in the diploid cells GOODMAN et coll (1968) observed diploid karyotype with one small F group chromosome and one ring chromosome in one third of the cells in a patient with primary polycythaemia that had developed into myelofibrosis

Reports on smaller groups of patients with primary polycythaemia comprising a few with clones were published by NOWELL & HUNGERFORD (1962) STAFFORD et coll (1965) and NOWELL (1965)

The series that affords the best basis for comparison with the present group of patients came from the Royal Marsden Hospital London and was published by KAY et coll (1966)

MILLARD et coll (1968) in a more recent survey of the above series examined more closely 7 cases with clones presenting deletion of an F group chromosome

At least 5 of the 11 untreated patients reported by KAY et coll had aneuploid clones

These authors recorded clones in addition to sporadic abnormalities in 11 of 32 patients treated Diploid clones were detected in 8 of these patients the remaining 3 patients suffered from leukaemia and had died at the time of survey of the series A great variety of chromosome abnormalities dominated by aneuploid clones had been revealed in these patients

The diploid clones presented varying karyotypes The authors emphasized in particular the finding of clones with deletion of an F group chromosome as the only abnormality that was detected in 4 of the 8 patients In the more recent

Table 2 *(cont)*

Patient No	Sample	Total analysed cells	Cells with aberrations	Clone	Abnormality*	Tentative explanation of aberrations
23	K	18	0			
24	K	49	94 % stable as clone c	c	46 XX 1?+ B— C— C— 16+ 16+ 16+	Deletion of one B and two C chromosomes trans location to chromosome No 1
	B	100	8 % unstable 10 % stable 4 as clone c			
25	K	50	2 % stable			
	B	8	0			

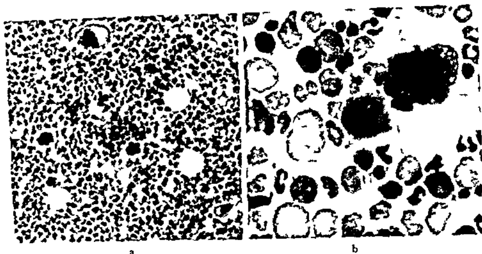
K bone marrow B peripheral blood * according to the Chicago Conference 1966

According to the definition of a clone, at least three cells must present characteristic and identical chromosome aberrations and these cells must possess no other chromosomal abnormalities All the 12 clones comprised many cells and amounted to 32 to 100 per cent of the cells analysed in the various bone marrow specimens

One clone, clone f, is fundamentally different from the remainder, its karyotype containing 47 chromosomes with an extra chromosome in the C group The remaining 11 clones had 46 chromosomes Table 2 presents the chromosomal pattern of the clones, as recorded during the analyses, with the nomenclature applied as suggested by the CHICAGO CONFERENCE (1966) It should however be pointed out that this description is of limited value without the quantitative extent of the aberrations A tentative explanation of the morphologic changes is offered in the last column of the table a quantitative assessment again cannot be expressed

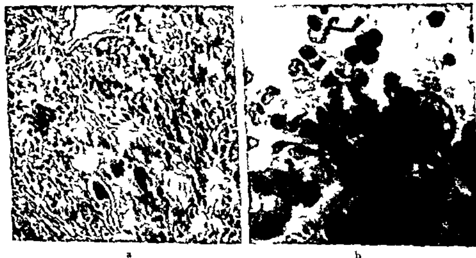
The question as to whether the karyotypes can be presumed to be balanced or not is more important than the morphologic descriptions of the chromosome aberrations An attempt has been made to assess this factor, but the present methodology of analysis has failed to answer this important question

It appears that the clones present were recorded in patients who had been treated for polycythaemia over prolonged periods of time No fundamental difference between the type of the clones in the various groups of patients has been recorded A possible correlation between clone formations and the stages of the disease will be discussed



a b

Fig 1 Patient No 6 a) Sternal bone marrow section Only *two fat cells in the field* general hyperplasia increased number of megakaryocytes no signs of fibrosis b) Bone marrow smear Normal distribution of haematopoietic cells no blast cells (Cf fig 5)



a b

Fig 2 Patient No 15 a) Sternal bone marrow section No fat cells in the field marked fibrosis and sign of sclerosis cluster of hypertrophic megakaryocytes b) Bone marrow imprint Many megakaryocytes in crushed marrow particle only few dissociated erythroblasts and granulocytes no blast cell (Cf fig 8)

report (MILLARD et coll.), it was stated that 7 patients had now been found to have deletion of an F group chromosome. It is pointed out that karyotypes with F deletion have occurred in other haematologic disorders. DE GROUCHY et coll. (1966), inter alia, had observed idiopathic sideroblastic anaemia with similar chromosome abnormality. MILLARD et coll. have investigated the excretion of tryptophan metabolites and have suggested that a correlation between the F aberration and abnormalities in the tryptophan metabolism may exist.

The appearance of the clones in the clinical groups. No clone formations appeared in untreated cases of primary polycythaemia (cf. Tables 1 and 2). The series however comprised only 4 patients of this category. As already stated, KAY et coll. had several aneuploid clones in their series of untreated patients.

Four clones were detected in the 9 treated patients without myelofibrosis, 4 clones were present in the 5 treated patients with myelofibrosis, and clones were evident in 4 of the 7 patients in whom incipient leukaemia was possible.

The aim of the classification was, inter alia, to decide whether any correlation exists between *the development of myelofibrosis and clone formation.* The figures may indicate an increased incidence of clones when the primary polycythaemia has developed into myelofibrosis, but the number of patients investigated is too limited to allow of any firm assessment, for example, a time factor may exert an influence.

As shown, the clones appeared only in treated patients. Most had received ^{32}P, a few either Myleran alone or a combination of Myleran and radiation treatment. One single clone carrying patient (No. 14) with myelofibrosis had had, in addition to Myleran, irradiation of the spleen. A more extensive series of *patients would be required in order to assess the conditions in patients* who had been treated with Myleran. It must be stated that a few patients had been given low doses of Myleran, although this is not mentioned in the table.

The tables enable the relationship between the formation of clones and the total amount of ^{32}P given to be evaluated. A survey does not present any clear picture of the conditions. The clones occur in the patients both after moderate and high doses of ^{32}P, whereas some patients who had received fairly high doses had not formed detectable clones.

The patients within each group have been listed in the tables according to the duration of disease. It appears from Table 2 that no clear correlation can be demonstrated between the duration of disease and the development of clones. However, it should be stated that it may be difficult to obtain definite information as to the time at which the first clinically relevant symptoms occur. KAY et coll. sometimes observed regression of the extent of the clones in relation to the treatment instituted. The present authors have had no possibility of assessing

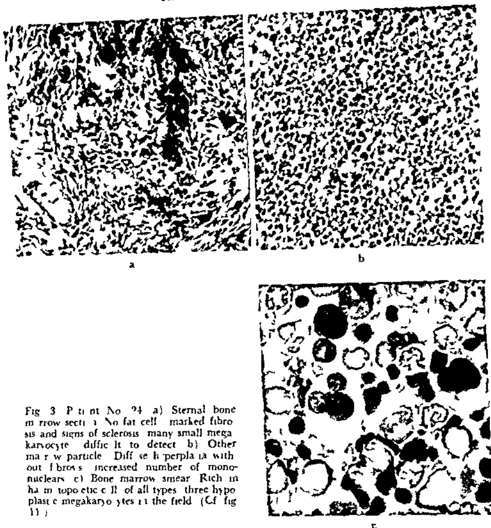


Fig 3 Patient No 24 a) Sternal bone marrow section No fat cell marked fibrosis and signs of sclerosis many small megakaryocyte difficult to detect b) Other marrow particle Diffuse hyperplasia without fibrosis increased number of mononuclears c) Bone marrow smear Rich in haemopoetic cell of all types three hypoplastic megakaryocytes in the field (Cf fig 11)

not be established at this stage although incipient transition into a leukaemic phase may be considered likely Fig 3 from patient No 24 is an example

The predominance of stem cells or immature atypical myeloid cells in the bone marrow is a definite sign of transition into the leukaemic phase at the same time examination of the peripheral blood will generally reveal leukocytosis and a high proportion of corresponding cell forms

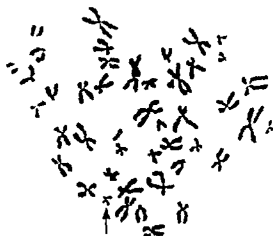
The types of clones detected in the groups of treated patients are presented in Table 2 Some of the karyotypes are shown in Figs 4 to 11 One of the 12 clones clone f presents a karyotype significantly different from the remainder

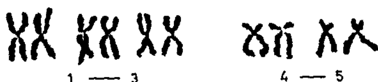
these conditions, since the investigations have not been continued over a sufficiently long period of time.

The histologic and cytologic appearances and the chromosomal pattern of the clones. Histologic and cytologic investigations of the bone marrow and of the peripheral blood are most important in establishing a diagnosis of primary polycythaemia and was applied during the classification of the patients. The bone marrow often presents characteristic appearances in non complicated instances. The *marrow is hyperplastic and contains a reduced number of fat cells.* The hyperplasia comprises both myelopoiesis, erythropoiesis and thrombocytopoiesis. The myelopoiesis presents a more or less marked displacement to the left. The hyperplasia of the erythropoiesis may be considerable and the cells present slight nuclear polymorphism. The most characteristic changes, however, occur in the thrombocytopoiesis in which the megakaryocytes are numerous, large and polymorphous, just as megakaryocytes in mitosis can be detected. As reported by FRANZEN et coll. (1961) from microplanimetric investigations, the size and *shape of the megakaryocytes* are important criteria in distinguishing various disorders within the myeloproliferative syndrome. Typical histologically non complicated appearances of primary polycythaemia in patient No. 6 are illustrated in Fig. 1.

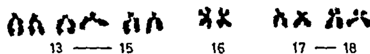
It is easy to detect the transition into myelofibrosis both in sections of bone marrow coagulates and *in smears from bone marrow.* In principle distinction should be made between two forms of fibrosis, i.e. diffuse fibrosis and sporadically localized fibrosis in which areas of fibrosis alternate with hyperplastic bone marrow of an appearance similar to that described above. Both forms of fibrosis may sometimes be demonstrated and transitory forms exist. In more advanced conditions, the fibrosis may be massive, and it may be difficult to prepare smears, the sections at this stage will present fibrous tissue in which large polymorphous megakaryocytes appear. A varying number of often rather *polymorphous reticulum cells and proliferating fibroblasts* will also be present. The myeloid cells will be sparse, appearing in stretches and accumulations, together with a few cells, derived from the erythropoiesis. Fig. 2 from patient No. 15 depicts this condition. With the appearance of bone marrow *fibrosis,* the peripheral blood may contain early forms of cells from the myelopoiesis and the erythropoiesis. This may give rise to diagnostic problems as regards leukaemia, but the cells are never atypical.

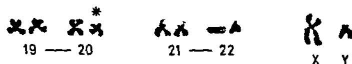
Leukaemia may develop in patients both with and without myelofibrosis. This usually occurs gradually, the disease not progressing rapidly until after a long period. There may be a shift to the left of the myelopoiesis for many years and an increased number of stem cells without any reduction in the erythropoiesis and the thrombocytopoiesis being evident. *The diagnosis of leukaemia can often*











: 5 Clone j Pat ent No 6 without myelofib osis Karyotype with deletion of an F group omosome (Cf fig 1)

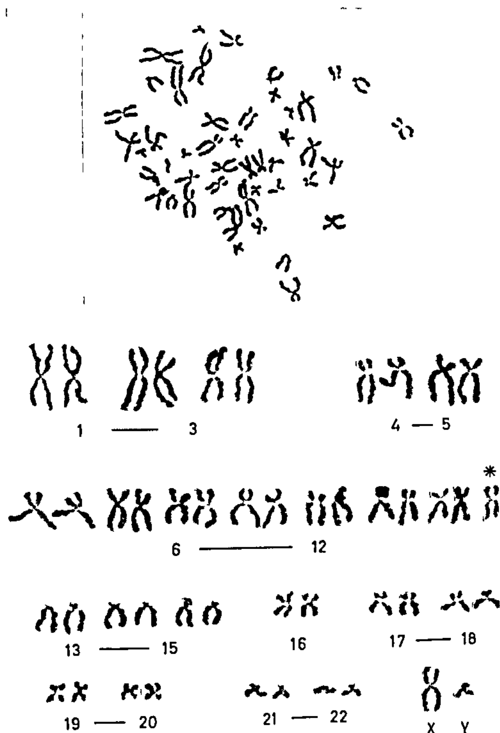


Fig 4 Clone f Patient No 12 without myelofibrosis Karyotype with 47 chromosomes registered as an extra C group chromosome

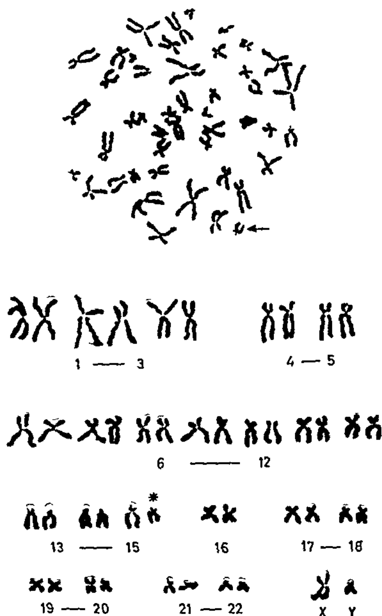


Fig. 7 Clone k. Patient No. 14 with myelofibrosis. Karyotype with deletion of a D group chromosome

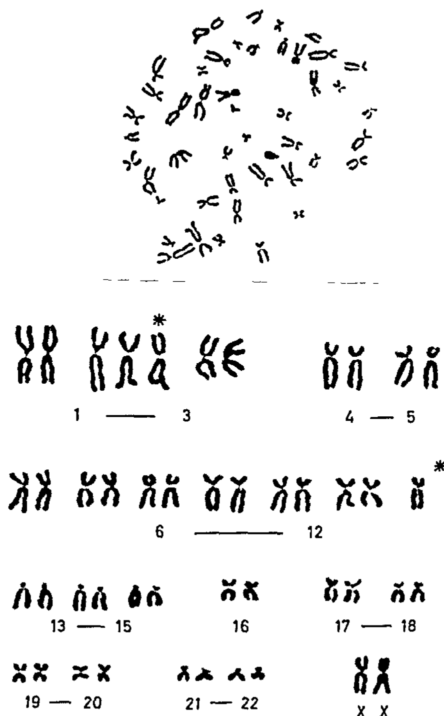


Fig 6 Clone 1 Patient No 13 without myelofibrosis Karyotype with translocation to a C group chromosome registered as an extra chromosome No 2

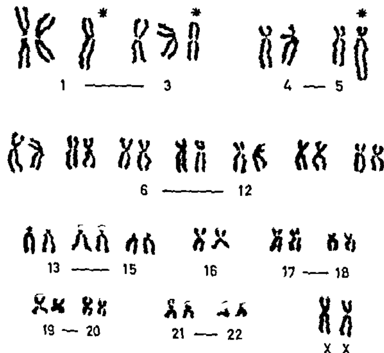


Fig 9 *Clone d* Patient No 21 with possible leukaemia Karyotype with translocation between chromosome No 2 and a B-group chromosome registered as a missing chromosome No 2 an extra chromosome No 3 and a marker *chromosome in the B-group*



Fig 8 Clone h Patient No 15 with myelofibrosis Karyotype with deletion of D and F group chromosomes Furthermore deletion of a C group chromosome registered as an extra D group chromo ome (Cf fig 2)

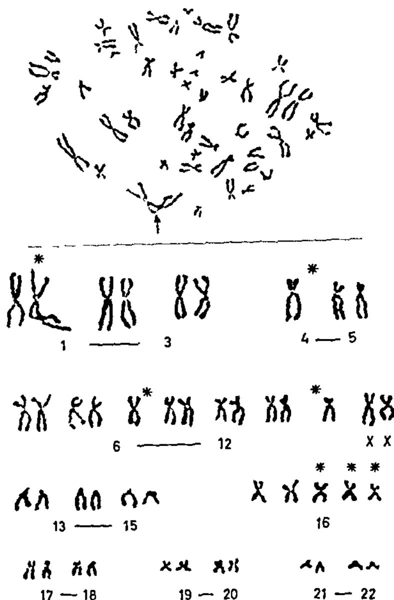


Fig 11 Clone c Patient No 24 with possible leukaemia Karyotype with deletion of B-group and two C group chromosomes and translocation to chromosome No 1 registered as a marker chromosome No 1 a missing B group and two missing C-group chromosomes and three extra chromosome No 16 (Cf fig 3)

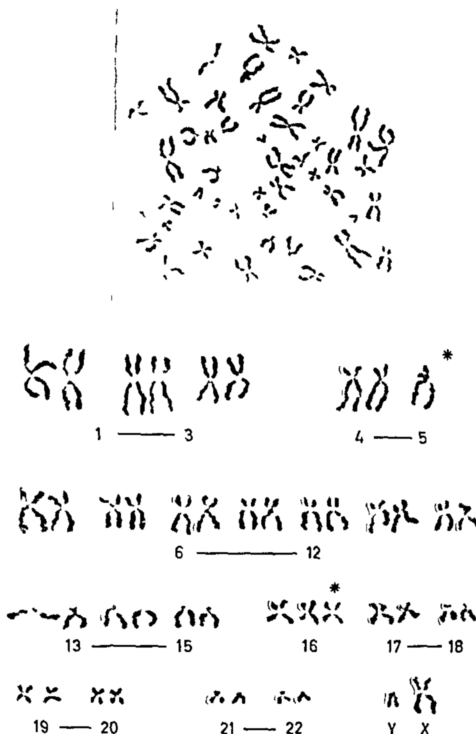


Fig 10 Clone a Patient No 22 with possible leukaemia Karyotype with deletion of B group chromosome registered as an extra chromosome No 16

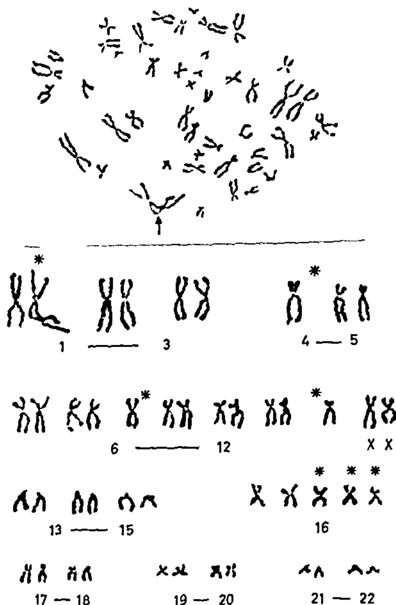


Fig 11 Clone c Patient No 24 with possible leukaemia Karyotype with deletion of B-group and two C group chromosomes and translocation to chromosome No 1 registered as a marker chromosome No 1 a missing B-group and two missing C group chromosomes and three extra chromosomes No 16 (Cf fig 3)

having a chromosome number of 47 with an extra C group chromosome, but no other abnormalities. The patient had primary polycythaemia without fibrosis and without transition into leukaemia. The remaining 11 clones presented diploid karyotypes with various structural chromosome aberrations with or without marker chromosomes. However, the types of the various aberrations were not fundamentally different in relation to the groups of patients from whom the clones originated. The types of aberrations have been viewed partly in relation to the clinical course and partly, as appears from the classification of the patients, in relation to the general histologic and cytologic bone marrow investigations.

The 12 clones comprise 4 clones with the deletion of an F group chromosome being the only abnormality of the karyotypes, and one clone in which the karyotype contains other aberrations, apart from an F deletion. The clones appear in all three groups of treated patients. KAY et coll. and MILLARED et coll. emphasized in particular the F deletion and discussed the importance of this aberration in primary polycythaemia. It seems most likely that there must be some relationship between primary polycythaemia and the F deletion when taking into consideration the high incidence in patients examined by the above authors and those in the present series. However, the F deletion has also been described in other haematologic disorders. DE GROUCHY et coll., inter alia, recorded the F deletion in several patients with sideroblastic anaemia and in one with subacute myeloid leukaemia. More detailed investigations of the possible importance of the F-group chromosome for the genesis of various haematologic disorders are consequently indicated.

The 4 clones in the 7 patients of the group in which transition into leukaemia was possible might represent malignant cell populations, since 3 of these patients died within six months after aspiration of bone marrow for chromosome analysis. It should be said in addition that the clones comprised from 50 to 100 per cent of the cells analysed in the samples, furthermore, 73 per cent clone cells were present primarily in one of the patients (No. 20) with clone b. This patient was treated with asparaginase without any clinical effect, after termination of this therapy the bone marrow investigation was repeated, and 100 per cent bone marrow cells of the clone type were then evident. The patient died from leukaemia about two months later.

The 4 clones in this group of patients were not fundamentally different from the remaining clones. Ph[1] chromosomes were not apparent in any of the clones. As to whether or not patients with primary polycythaemia may develop chronic myeloid leukaemia has been much discussed. It appears to the present authors that this never occurs or at any rate extremely rarely, and so far the chromosome analyses support this contention. From a clinical point of view, the leukaemic phase presents the appearances of acute or subacute myeloid leukaemia.

Other authors have described clone formation in primary polycythaemia in the leukaemic phase. Apart from diploid clones of the same type as those mentioned in this report, a number of authors have observed aneuploid clones. KAY et coll. described three patients with primary polycythaemia in the leukaemic phase — in all of whom aneuploid clones were detected. KEMI et coll. (1962), NOWELL & HUNGERFORD (1962), ERKMAN et coll. (1967), NOWELL (1965) and KOLLISCHER et coll. (1967) all recorded occasional aneuploid clone formations in the leukaemic phase although the groups of patients examined also presented diploid clones with abnormal chromosomal patterns and a few were included in which a Ph[1] chromosome was claimed to be present.

Comparison between chromosomal pattern in clones in primary polycythaemia and acute leukaemia and after irradiation. As most patients with primary polycythaemia are treated with ^{32}P and since an appreciable number enter a leukaemic phase, it appears natural to correlate the chromosomal patterns occurring in the clones in primary polycythaemia, acute leukaemia as well as after irradiation. A further examination of the conditions in acute leukaemia was outside the scope of the present investigation but it is a well known fact that in almost half of the cases of acute leukaemia clones with abnormal karyotypes occur; these clones (cf. JENSEN 1969) are almost always aneuploid and mainly hyperploid. Irradiation may give rise to formation of clones which are usually diploid with an abnormal chromosome pattern with or without marker chromosome. This was demonstrated by VISFELDT (1966) inter alios who demonstrated the development of diploid clones with abnormal karyotypes in tissue cultures from irradiated human skin. All these clones seemed to be balanced, i.e. the karyotypes contained the normal total amount of chromatin. It therefore seems to be particularly interesting to consider whether the clones evident in patients with primary polycythaemia following long term treatment with ^{32}P are balanced. As already stated, 11 of the 12 clones detected in the present material contained a diploid karyotype, and the authors have tried on a morphologic basis to assess whether they were balanced. The methodology applied at present in chromosome analysis allows of only a limited evaluation of the rearrangement of the chromosome material inter alia because the classification of the individual C-group chromosomes is uncertain. The writers are unable to decide with certainty whether the karyotypes are balanced or not. If they are balanced it would appear that this would support the hypothesis that the aberrations are primarily radiation induced as a result of ^{32}P therapy. As stated previously, many authors have reported on the finding of aneuploid clones in primary polycythaemia at various stages, even in untreated patients, and consequently not all the clones can be radiation induced. The conditions

are thus far from being unambiguous. However, should it appear that treatment with ^{32}P gives rise to the appearance of chromosomally abnormal cells with selective advantages — and from numerous observations it is evident that cells with abnormal chromosome pattern have an increased tendency to malignancy (e.g. VISFELDT 1967) — then the chromosome studies may contribute to an understanding of the increased incidence of acute leukaemia in primary polycythaemia. The possibility can also not be overlooked that chromosome analysis may be of importance as regards choice of therapy when it has been revealed how the chromosome pattern appears after treatment with other agents.

Conclusion

The series comprising 25 patients was classified into four categories: 4 untreated patients, 9 treated without myelofibrosis, 5 treated with myelofibrosis, and 7 treated patients in whom incipient transition into a leukaemic phase was possible on clinical grounds. A total of 12 clones occurred in the bone marrow aspirates in the three groups of treated patients, four in each group. Apart from a doubtful predominance in the group with fibrosis, no differences were detected at the various stages of development of primary polycythaemia.

Of the 12 clones, 11 were diploid with varying chromosome patterns, and one contained 47 chromosomes but presented no other abnormalities. An F group chromosome was abnormal in 5 clones. No correlation was apparent between the types of aberrations recorded and the histologic and cytologic bone marrow findings in the various groups.

Clones appearing in acute leukaemia are generally aneuploid and were thus distinguished from 11 of the 12 clones detected in the material. At the same time, however, other authors have recorded aneuploid clones at various stages of primary polycythaemia, in particular in the leukaemic phase. Radiation induced clones in other studies seem generally to be diploid and at the same time to present a balanced chromosomal pattern. A survey of the diploid clones in the present material does not allow of any definite conclusions as to whether the clones were balanced. The possible radiation induction of the clones and the importance of an abnormal chromosome pattern as a tendency to malignancy of the cells are discussed in connection with the increased incidence of leukaemia in patients with primary polycythaemia treated with ^{32}P.

Acknowledgements

The authors are indebted to Miss Grethe Jensen for technical assistance. The work was assisted by grants from the Danish State Research Foundation.

SUMMARY

Twenty five patients with primary polycythaemia were investigated Chromosome analyses of bone marrow and peripheral blood revealed clone formation in 12 of the patients The chromosomal pattern of the clones was correlated to the histologic and cytologic bone marrow appearances A possible relationship between clone formation 32P therapy and the development of leukaemia is discussed

ZUSAMMENFASSUNG

Die Untersuchung umfasst 25 Fälle von primärer Polycythaemie Bei Chromosomen Analysen des Knochenmarks und des peripheren Blutes wurde in 12 Fällen eine Clone Bildung gefunden Das chromosomale Bild dieser Clones wird zu den histologischen und cytologischen Knochenmarksstudien in Beziehung gestellt Der mögliche Zusammenhang zwischen der Clone Bildung der 32P Therapie und der Entwicklung von Leukämie wird diskutiert

RÉSUMÉ

Les auteurs ont examiné vingt cinq malades atteints de polycythémie primitive L'étude chromosomique de la moelle osseuse et du sang périphérique a montré la formation de clones chez 12 de ces malades Le type chromosomique des clones est en rapport avec les aspects histologiques et cytologiques de la moelle osseuse Les auteurs discutent la possibilité d'une relation entre la formation des clones le traitement par le 32P et l'apparition d'une leucémie

REFERENCES

BRAUNSTEINER H ROTHENBUCHNER G und SCHOBER B Kann eine Polycythaemia vera in eine chronische myeloische Leukämie übergehen? Med Klin 59 (1964) 614

CHICAGO CONFERENCE Standardization in human cytogenetics Birth defects Original Article Series II p 1 The National Foundation New York 1966

ENGEL W MERKER H SCHNEIDER G and WOLF U Clonal occurrence of a chromosome Dq in myelosclerosis with myeloid metaplasia Humangenetik 6 (1968) 335

ERKMAN B HAZLETT B CROOKSTON J H and COWEN P E Hypodiploid chromosome pattern in acute leukemia following polycythemia vera Cancer 20 (1967) 1318

FRANZEN S STRENGER G and ZAJICEK J Microplanimetric studies on megakaryocytes in chronic granulocytic leukaemia and polycythaemia vera Acta haemat 26 (1961) 182

GOODMAN R M BOURONCLE B A MILLER F and NORTH C Unusual chromosomal findings in a case of myelofibrosis J Hered 59 (1968) 348

DE GROUCHY J DE NAVA C ZITTOUN R et BOUSSER J Analyses chromosomiques dans l'anémie sidéroblastique idiopathique acquise Nouv Rev franç Hémat 6 (1966) 367

JENSEN M K Chromosome studies in potentially leukaemic myeloid disorders Acta med scand 183 (1968) 535

— Chromosome studies in acute leukaemia p 28 Munksgaard Copenhagen 1969

KAY H E M LAWLER S D and MILLARD R E The chromosomes in polycythaemia vera Brit J Haemat 12 (1966) 507

KEMP, N. H., STAFFORD, J. L. and TANNER, R. K.: Cytogenetic studies of polycythaemia vera. 8th Congress European Soc. of Hematology, Vienna 1961, p. 92. Karger, Basel 1962.

KIOSSOGLOU, K. A., MITUS, W. J. and DAMESHEK, W.: Cytogenetic studies in the chronic myeloproliferative syndrome. Blood 28 (1966), 241.

KOULISCHER, L., FRUHLING, J. et HENRY, J.: Observations cytogénétiques dans la maladie de Vaquez. Europ. J. Cancer 3 (1967), 193.

LEVAN, A., NICHOLS, W. W., HALL, B. et coll.: Mixture of Rh positive and Rh negative erythrocytes and chromosomal abnormalities in a case of polycythemia. Hereditas 52 (1964), 89.

MACDIARMID, W. D.: Chromosomal changes following treatment of polycythaemia with radioactive phosphorus. Quart. J. Med. 34 (1965), 133.

MILLARD, R. E., LAWLER, S. D., KAY, H. E. M. and CAMERON, C. B.: Further observations on patients with a chromosomal abnormality associated with polycythaemia vera. Brit. J. Haemat. 14 (1968), 363.

MOORHEAD, P. S., NOWELL, P. C., MELLMAN, W. J. et coll.: Chromosome preparations of leucocytes cultured from human peripheral blood. Exp. Cell Res. 20 (1960), 613.

NAGY, G. and YURCUTIS, R. P.: Chromosome studies on patients with polycythaemia vera. *Haematologia (Budap.) 2 (1968), 179.*

NOWELL, P. C.: Prognostic value of marrow chromosome studies in human preleukemia. Arch. Path. 80 (1965), 205.

— and HUNGERFORD, D. A.: Chromosome studies in human leukemia. IV. Myeloproliferative syndrome and other atypical myeloid disorders. J. Nat. Cancer Inst. 29 (1962), 911.

SOLARI, A. J., SVERDLICK, A. B. and VIOLA, E. R.: Chromosome abnormality in myeloid metaplasia. Lancet 1962 II, p. 613.

STAFFORD, J. L., KEMP, N. H. and TANNER, R.: Cytogenetics and *the assessment of marrow* dyscrasia. *In*: Current research in leukaemia, p. 77. Edited by F. G. J. Hayhoe. University Press, Cambridge 1965.

TJIO, J. H. and WHANG, J.: Chromosome preparations of bone marrow cells without prior in vitro culture or in vivo colchicine administration. Stain Technol. 37 (1962), 17.

VISFELDT, J.: Radiation induced chromosome aberrations in human cells. Risø Report No. 117 (1966), p. 51.

— Kromosomaberrationer og malignitetsudvikling. (In Danish.) Nord. Med. *78 (1967), 1285.*

— FRANZEN, S. and FRIBUKAIT, B.: Cytogenetic studies in myeloproliferative syndrome and some atypical myeloid disorders. Acta path. microbiol. scand. Section A 78 (1970), 80.

FROM THE DIVISION OF RADIOBIOLOGY (DIRECTOR DOCENT A NILSSON), THE RESEARCH INSTITUTE OF NATIONAL DEFENCE SUNDBYBERG SWEDEN

PATHOLOGIC EFFECTS OF DIFFERENT DOSES OF RADIOSTRONTIUM IN MICE

Development and incidence of leukaemia

by

AGNAR NILSSON

Interest in radiation induced leukaemia has mostly been concentrated on leukaemia developing after external irradiation It has however, been reported (1—4 8—11 15—18) in different animal species that internal emitters can also induce various types of leukaemia Internal emitters such as radiostrontium have different consequences for the haematopoietic system compared with those of external irradiation (10 14) Radiostrontium rapidly concentrates in the skeleton and will thus for a considerable time almost exclusively irradiate the bone marrow Extraskeletal parts of the haematopoietic tissue are on the other hand only slightly and mainly indirectly influenced by radiostrontium These facts seem to offer problems of interest particularly concerning the site of origin development and relation between dose and incidence of leukaemia

The present report deals with some of these aspects following the administration of different doses of ^{90}Sr to mice

Material and Methods The investigation comprised 1 430 CBA mice 75 ± 5 days old they were divided into two main series series I and series II The mice in each series were separated into different groups and were injected intraperi

Submitted for publication 1 December 1969

Table 1

Experimental conditions and the ^{90}Sr doses employed

Dose of ^{90}Sr $\mu Ci/g$ body *weight*	Total number of mice investigated	Number of mice killed in groups of five	Last day of sacrifice	Number of mice that died before sacrifice was due
Series I				
1 6	120*	65	300	50
0 8	121	75	360	46
0 4	122	95	480	27
0 2	122**	103***	540	17
Control	95	91****	570	1
Series II				
1 2	50	—	—	50
0 8	100	—		100
0 7	400	—		400
0 6	50	—		50
0 4	100	—		100
0 2	50	—		50
Control	100	—		100

Of these animals 5* and 2** were lost during the experiment only 3*** and 4**** animals respectively were sacrificed in the last test group

toneally with various doses of $^{90}Sr(NO_3)_2$, in accordance with the data given in Table 1

All the mice were kept in plastic cages, ten mice in each, and given a standard diet

In series I five mice from each of the different dose groups and from the untreated control group were sacrificed after 7, 14, 21 and 30 days, and then at monthly intervals until all mice were used up Many mice in this series died however before their time of sacrifice (Table 1) The mice before sacrifice were anaesthetized for blood analysis, the blood being obtained with a Pasteur pipette from the medial venous plexus of the eye The femora, tibiae and humeri as well as the pelvic bones spine thymus spleen mesenteric lymph node, liver kidneys and the brain, for the histologic investigation, were fixed in Stieve's fluid They were prepared according to conventional histologic method, stained routinely by the van Gieson method, haematoxylin and eosin, Lillie's azure eosinate and PAS according to Hotchkiss

The mice in series II were collected from earlier ^{90}Sr experiments devised to investigate long term effects of ^{90}Sr The number of mice and the doses of ^{90}Sr

Table 2

Type and frequency of leukaemia induced by the different doses of ^{90}Sr

Dose μC/g	Number of mice	Thymic lymphomas	Bone marrow lymphomas	Generalized lymphomas	Myeloid leukaemia	Chronic lymphocytic leukaemia	Frequency of leukaemia
Series I							
1.6	115	1	1				1.7
0.8	121	—	3	—	1	—	3.3
0.4	127	2	4	5	—	1	9.8
0.2	120	2	2	—	—	—	3.3
0.0	95	—	—	—	—	—	
Series II							
1.2	50	2	—	2	—	—	8.0
0.8	100	1	6	—	—	—	0
0.7	400	9	8	5	—	—	5.5
0.6	50	1	5	—	—	—	12.0
0.4	100	3	20	—			23.0
0.2	50	—	11	3	—	—	28.0
0.0	100	—	—	1	—	—	1.0

Site of origin could not be determined

employed are given in Table 1 The mice in this series were allowed to survive for their total life span and special care was taken to detect leukaemia All the mice were examined post mortem and investigated by conventional histologic and haematologic methods

Results

Incidence of leukaemia

In series I in spite of the great number of mice sacrificed in each of the different dose groups (Table 1) only four cases of leukaemia were found two in each of the 1.6 and 0.4 μCi groups Among a total of 140 mice in series I which died before sacrifice 18 cases of leukaemia were detected It is notable that among the 50 mice in the 1.6 μCi group which died before sacrifice none died from leukaemia In the other groups four of 46 ten of 27 and four of 17 developed leukaemia in the 0.8 0.4 and 0.2 μCi groups respectively No leukaemia was observed in the control group

In series II a total of 76 mice developed leukaemia The highest frequency (28 %) occurred among animals in the 0.2 μCi group and a slightly lower

Table 3

Data on the mice from which blood samples were obtained

Series	Type of leukaemia and dose employed μCi/g body weight	Mouse number	Weight of		Bone marrow degree of leukaemia proliferation	Peripheral blood	
			Spleen mg	Thymus mg		Number of white cells	Haemoglobin g/100 ml blood
	Bone marrow lymphoma						
I (sacrificed)	1.6	I 55	83.5	31.3	1	1 000	10.6
I (died) in agonae	0.4	I B 6	82.4	6.7	2	660	10.4
I (died)	0.4	I B 2	128.6	73.8	3	230	4.3
I (sacrificed)	0.4	I 40b	224.0	26.0	2	5 320	7.8
II (died)	0.7	II 32	882.4	28.3	3	28 720	5.9
	Thymic lymphoma						
I (sacrificed)	1.6	I 57	227.9	181.2	0	1 240	9.9
II (died)	0.7	II 75	645.6	350.4	0	8 260	7.2
	Generalized lymphoma						
I (died)	0.4	I B 7	264.2	93.5	3	7 340	12.6
II (died)	0.7	II 122	1 080.1	301.2	3	30 100	4.8

0— No signs of leukaemia proliferation 1— only thoracic vertebrae involved 2— most marrow cavities involved 3— most marrow cavities involved infiltration lymphoma around thoracic vertebrae

figure (23 %) was arrived at for the 0.4 μCi group (Table 2) One case of leukaemia was detected in the control material

Type of leukaemia

Of the total of 98 cases of leukaemia in series I and II, 97 probably arose from the lymphatic cell series These were defined according to their location and probable site of origin either as bone marrow lymphomas or thymic lymphomas Cases in which it was impossible to determine the site of origin on account of widespread infiltration in various tissues were designated as generalized lymphoma Sixty were bone marrow lymphomas, twenty one thymic lymphomas and fifteen generalized lymphomas One case of chronic lymphatic leukaemia and one of myeloid leukaemia were also recorded

Bone marrow lymphoma Only two cases were observed among the sacrificed mice in series I, one each in the 1.6 and 0.4 μCi groups Among the mice that



Fig 1 Sections from mouse of series I killed 240 days after injection of 1 6 μCi ^{90}Sr/g body weight Lymphoma arising from marrow in thoracic vertebra lymphoid cell proliferation also in two other thoracic vertebrae van Gieson × 30 (Weight of spleen 83 5 mg of thymus 31 3 mg number of leukocytes 1000/mm haemoglobin 10 6 g/100 ml)

died before sacrifice eight bone marrow lymphomas were detected in series I and fifty in series II (Table 2)

The primary site of leukaemic proliferation was almost exclusively inside the bone marrow Proliferation of lymphoid elements was detected predominantly within the thoracic vertebrae and the sternum generally in areas inside one or more of the former (Fig 1) Other parts of the marrow were probably not involved but proliferation occurred successively in most parts of the marrow (Fig 2) as well as infiltration into extramedullary tissues This was the case particularly around the thoracic vertebrae where lymphomas were common (Fig 3a) The lymph nodes were usually unaffected but could sometimes be infiltrated and enlarged to a varying degree

The thymus was not infiltrated with leukaemic cells (Figs 2b and 3b) or only lightly to moderately so histologically giving the impression of being metastases The mean weight of the thymus was 33 9 ± 4 44 mg The normal mean weight of the thymus among the non leukaemic mice in the corresponding age groups was in the 1 6 μCi group 6 8 ± 1 6 mg in the 0 8 μCi group 12 8 ± 1 9 mg in the 0 4 μCi group 15 5 ± 1 9 mg and in the 0 2 μCi group 16 0 ± 1 7 mg The thymus in 61 7 % of the 60 cases of bone marrow lymphomas weighed less than 16 0 mg in 18 3 % between 16 1 and 48 0 mg and in 20 % between 48 1 and 95 1 mg

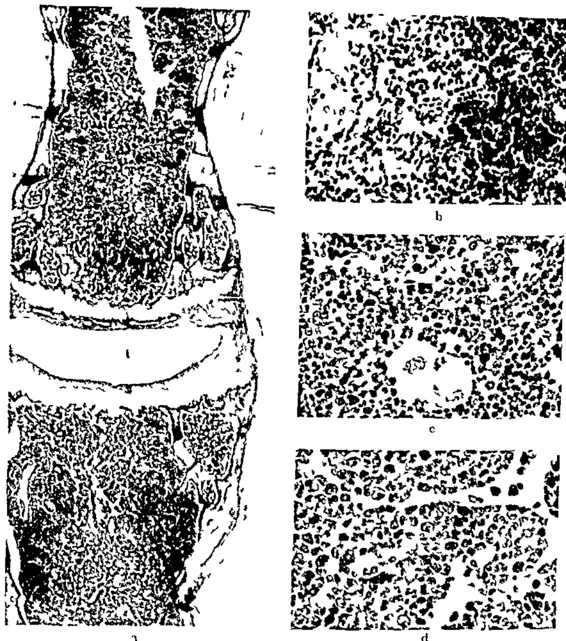


Fig. 2. Sections from mouse of series I killed 150 days after injection of 0.4 μCi ^{90}Sr/g body weight. Most marrow cavities filled with proliferating lymphoid cells. (Weight of spleen 244.0 mg, of thymus 26.0 mg, number of leukocytes 9320/mm^3, haemoglobin 7.8 g/100 ml.) a) Lumbar vertebrae with tightly packed lymphoid cells. No infiltration of cells outside the marrow cavities. van Gieson ×50. b) Thymus with normal histologic appearance. H. & E. ×500. c) Spleen with heavy proliferation of lymphoid cells. Megakaryocytes and erythroid elements still remain. H. & E. ×500. d) Magnification of marrow from same detail as in (a). Actively proliferating lymphoid cells. H. & E. ×1250.

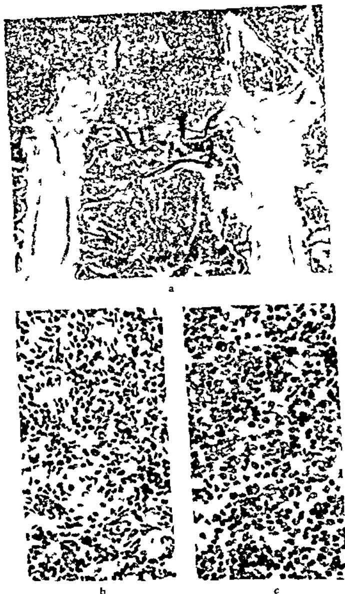


Fig. 3. Sections from mouse of series I that died 216 days after injection of 0.4 μCi ^{90}Sr/g body weight. All marrow cavities filled with proliferating lymphoid cells. (Weight of spleen 82.4 mg, of thymus 6.7 mg, number of leukocytes 660/mm^3, haemoglobin 10.4 g/100 ml.) a) Lymphoma infiltrating the tissues outside a thoracic vertebra. van Gieson ×50. b) Thymus. Marked lymphocyte depletion. H. & E. ×500. c) Spleen. Extensive lymphoid cell proliferation. H. & E. ×500.

The spleen was enlarged by increasing lymphoid proliferation in the red pulp but extensive extramedullary haematopoiesis usually existed (Figs 1, 2 and 3) The mean weight was 301 8 ± 24 3 mg (range 82 4—1 044 3 mg) compared with a mean weight for non leukaemic mice of the same age of 91 3 ± 5 8 mg in the 1 6 μCi group, 65 8 ± 3 7 mg in the 0 8, 71 4 ± 7 8 mg in the 0 4, and 62 7 ± 2 8 mg in the 0 2 μCi group

Apart from the two sacrificed mice, blood samples were obtained only from a few mice killed in agonae (Table 3)

Thymic lymphoma Twenty one of this type were observed, only one of which was among the sacrificed mice (Table 2) The primary leukaemic process seemed to have its site in the thymus (Fig 4) In contrast to the bone marrow lymphomas, the thymus was generally much enlarged, usually it was the size of a hazelnut or larger and was adherent to the structures of the thoracic cavity Its mean weight was 308 8 ± 69 7 mg (range 22 1—830 6) The spleen was often enlarged (*mean weight 282 5 ± 35 0, range 72 0—518 4*) and *infiltrated* with lymphoid cell elements Islands of compensatory haematopoietic activity generally remained, however The bone marrow and lymph nodes were infiltrated to varying degrees One blood sample was obtained from a mouse killed in agonae (Table 3)

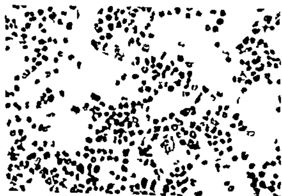
The spleen was slightly affected or unaffected (mean weight 72 2 mg) in two cases, both in series II, in three other cases (series I and II) it was only slightly infiltrated (mean weight 121 1 mg) The bone marrow was not infiltrated in these cases

Generalized lymphoma It was impossible to determine the site of origin of the leukaemic process in 15 cases (five among the mice which died before sacrifice in series I, and the remainder in series II) The process *was generalized to many* organs (liver, kidneys, brain, spinal cord, muscles) outside the haematopoietic system A heavy proliferation of lymphoid cells was seen in the bone marrow, as well as infiltration, particularly of the muscles surrounding the thoracic spine The thymus was enlarged (mean weight 131 7 ± 24 4 mg range 18 3—320 3 mg) together with the spleen (mean weight 564 4 ± 98 5 mg, range 178 6—1 832 0 mg) and lymph nodes Blood samples were obtained from two mice killed in agonae (Table 3)

One case of *chronic lymphocytic leukaemia* occurred among the sacrificed mice in the 0 4 μCi group 420 days after ^{90}Sr injection The spleen was infiltrated with lymphoid elements In all the bone marrow cavities, a large number of small circumscript foci of lymphoid cells occurred, scattered in an otherwise markedly hypoplastic marrow Many mastocytes were present in the marrow as well as in



a



b

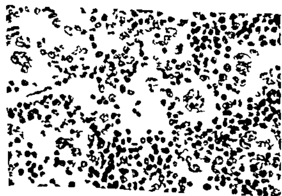


Fig 4 Sections from mouse of series II that died 150 days after injection of 0 7 μCi ^{90}Sr/g body weight No lymphoid cell proliferation in the bone marrow or spleen (Weight of spleen 85 4 mg of thymus 2[illegible] 1 mg) a) Thymic lymphoma with heavy uniform proliferation of lymphoid cells H & E ×500 b) Bone marrow of thoracic vertebrae Hypoplasia and no lymphoid cells van Gieson × [illegible]00 c) Spleen Intense erythro and megakaryocytopoiesis H & E ×500

Table 4

Latency time for lymphoma development

Dose μCi/g body weight	Number of mice with lymphoma	Latency time days	Latency time days and total number of			
			Lymphomas n = 96	Bone marrow lymphomas n = 60	Thymic lymphomas n = 21	Generalized lymphomas n = 15
Series I						
1.6	2	255				
0.8	3	250				
0.4	11	240±20.9				
0.2	4	252				
Control	0	—				
			237±5.8	221.2±7.6	254.3±10.1	243.5±14.1
Series II						
1.2	4	285				
0.8	7	200				
0.7	22	221±9.2				
0.6	6	216				
0.4	23	222±11.2				
0.2	14	262±20.8				
Control	1	806				

other organs. The number of white cells in the peripheral blood was 46 500 (95 % lymphoid cells, 3 % monocytes and 2 % granulocytes).

One case of *myeloid leukaemia* was detected in a mice in the 1.6 μCi group (series I), one of those which died before sacrifice. Myeloid leukaemia was characterized by heavy proliferation of mostly mature granulocytic elements in the bone marrow, spleen and lymph nodes. The liver, muscles around the spine, and the membranes of the spinal cord were heavily infiltrated as well. The thymus, weighing only 1.4 mg, was not affected.

Latency time

The mean latency time for the total lymphoma material (n = 96) in series I and II was 237.8 ± 5.8 days. The case of myeloid leukaemia appeared at 352 days and the case of chronic lymphatic leukaemia at 420 days (Table 4).

The generalized lymphoma detected among the control animals in series II appeared after 806 days.

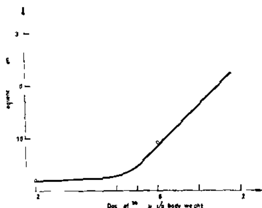


Fig 5 Percentage of bone marrow lymphomas by dose in series II

No relation between dose and latency time appeared to exist for lymphomas (Table 4) Nor was there any difference between thymic lymphoma (254 3 ± 10 1 days) bone marrow lymphoma (221 2 ± 7 6 days) and generalized lymphoma (243 5 ± 14 1 days)

Discussion

Leukaemia occurred in all of the dose groups employed in this investigation Out of a total of 98 cases 96 were lymphomas one of myeloid leukaemia and one of chronic lymphatic leukaemia Sixty (62 5 %) of the lymphomas seemed to have originated within the bone marrow primarily as localized bone marrow lymphoma (Fig 1) The occurrence of lymphomas in the bone marrow was inversely related to dose since the frequency was less great in the higher than in the lower dose groups (Fig 5)

Twenty one (20 8 %) of the lymphomas detected appeared to arise in the thymus No relation to dose seemed to exist but the material is too small to allow any definite conclusions In 15 cases (15 6 %) of generalized lymphoma it was impossible to decide from which tissue the lymphomas were derived

The mean latency time in the various dose groups did not differ in this material (Table 4) Nor were there any differences in this respect between lymphomas arising in the bone marrow or in the thymus Earlier work (14) has indicated that the highest doses of ^{90}Sr employed have a most destructive effect on the bone marrow Most of the haematopoietic function is taken over by the spleen and bone marrow regeneration occurs only to a limited extent and particularly at certain sites such as in the thoracic vertebrae and sternum where the dose

absorbed is smaller than in larger bones, e g the long bones In the lower dose groups the marrow is severely damaged initially but its capacity for regeneration is better preserved Thus, with decreasing dose an increased number of living but damaged cells will occur That the most favourable site for regeneration is in the smaller bones may therefore explain the start of lymphomas at multicentric sites, particularly within the thoracic vertebral and sternal marrow (Fig 1)

WATANABE (18) in an earlier paper, assuming the development of leukaemia from the bone marrow, suggested that these changes take place first in certain parts of the bone marrow and thereafter spread to other parts and finally to other organs and tissues He assumed that the most favourable sites for the start of leukaemia might be within the vertebral marrow He also noticed a tendency to early infiltration of the tissues surrounding the vertebrae (17) Those suggestions and observations agree with the findings in the present investigation, though these could also indicate a *multicentric genesis within the bone marrow*, however

The findings concerning the genesis of ^{90}Sr induced leukaemia in this work are very different from those after fractionated, external, total body irradiation Of the leukaemia cases described in the literature after fractionated, whole body irradiation the majority represent lymphomas of the thymus, the latency time of which is much shorter than in those of non thymic origin (6) This discrepancy may have been caused by differences in age and mode of irradiation In the present investigation all the mice were 75 days old Fractionated irradiation *yields thymic lymphomas at an optimum rate only when young mice* are irradiated After injection of ^{90}Sr, the bone marrow is the haematopoietic tissue which is most subject to risk The marrow is continuously irradiated but the degree of damage and regeneration in its various parts differ Other parts of the haematopoietic system are on the other hand not damaged initially to the same extent as after external irradiation Above all, the thymus is obviously not affected to the same degree as after external irradiation, and the regeneration *is not so evident Preliminary* results with ^{90}Sr (7) have indicated that regeneration disturbances (early asymmetry) *do not occur among young mice*, which is of interest since these asymmetries have been assumed by JARPLID (6) to be phenomena associated with the induction of thymic lymphoma That these changes did not appear in the present material may be connected with a lesser need of, and a better supply of, cells competent to repopulate the thymus

The role of the spleen in relation to the bone marrow and the thymus in leukaemogenesis cannot be established from this investigation The importance of the spleen as a source of compensatory haematopoiesis with increasing dose of ^{90}Sr is, however, apparent *It has also been shown by* JACOBSON (5) that the haematopoietic reserve offered by the spleen is one factor determining the survival of the mice, since the mortality increases among splenectomized irradiated mice

SUMMARY

Varying doses of ^{90}Sr were administered to 1 430 CBA mice about 75 days old to investigate the site of origin development and relation between the dose and incidence of leukaemia The significance of the bone marrow particularly of the thoracic vertebrae as the site of origin of leukaemia and its relationship to the thymus and spleen in this respect as well as following irradiation are considered in turn

ZUSAMMENFASSUNG

Verschiedene Dosen von ^{90}Sr wurden an 1 430 75 tage alten CBA Mausen verabreicht um Ursprungsstelle Entwicklung und Verhaltnis zwischen der Dosis und der Entwicklung von Leukamie zu studieren Die Bedeutung des Knochenmarkes besonders in der dorsalen Wirbelsaule als Ursprungsstelle der Leukamie und deren Verhaltnis zu Thymus und Milz in dieser Hinsicht sowie nach Bestrahlung werden diskutiert

RÉSUMÉ

L auteur a administre des doses variees de ^{90}Sr à 1430 souris CBA agees de 75 jours environ pour etudier le lieu de l origine le devoloppement et la relation entre la dose et la frequence de la leucemie Il étudie l importance de la moelle osseuse en particulier celle des vertebres dorsales comme siege de l origine de la leucemie et il etudie ses rapports avec le thymus et la rate à ce point de vue ainsi qu apres l irradiation

REFERENCES

1 BOEGLER F und KRIEGEL H Leukamoide Reaktion nach 90 Strontium Inkorporation bei Ratten Blut 17 (1968) 345
2 CASARETT G W TUTTLE L W and BAXTER R C Pathologic effects of ingested strontium 90 in rats and monkeys UR 597 University of Rochester New York 1961
3 COSGROVE G E and UPTON A C Some late effects of radiostrontium in RF male mice J nucl Med 3 (1962) 293
4 ITO T YOKORO K ITO A and NISHIHARA E A comparative study of the leukemogenic effects of strontium 90 and X Rays in mice (33 553) Proc Soc exp Biol 130 (1969) 345
5 JACOBSON L O The hematologic effects of ionizing radiation *In* Radiation biology Volume 1 p 1029 Edited by A Hollaender McGraw Hill Book Company New York Toronto London 1954
6 JARPLID B Radiation induced asymmetry and lymphoma of thymus in mice Acta radiol (1968) Suppl No 279
7 — Personal communication (1969)
8 MCCLELLAN R O Hematopoietic tissue neoplasms in animals administered 90 Sr Hlth Phys 12 (1966) 1362
9 — and RUPPRECHT F C Section I Dose-effect studies Toxicity of inhaled $^{90}SrCl_2$ in beagle dogs LF 38 Lovelace Foundation Albuquerque New Mexico 1967
10 NILSSON A Effects of radiostrontium on the blood and haematopoietic tissues of mice Acta vet scand 3 (1962) 103

11 — Influence of gestation and lactation on radiostrontium induced malignancies in mice I Incidence distribution and characteristics of ^{90}Sr induced malignancies Acta radiol Ther Phys Biol 6 (1967) 33
12 — Pathologic effects of different doses of ^{90}Sr in mice Development of carcinomas in the mucous membranes of the head Acta radiol Ther Phys Biol 7 (1968) 27
13 — Pathologic effects of different doses of radiostrontium in mice Dose effect relationship in ^{90}Sr induced bone tumours Acta radiol Ther Phys Biol 9 (1970) 155
14 — Pathologic effects of different doses of radiostrontium in mice Changes in the haematopoietic system Acta radiol Ther Phys Biol 9 (1970) 528
15 VAN PUTTEN L M and DE VRIES M J Strontium 90 toxicity in mice J nat Cancer Inst 28 (1962) 587
16 THOMAS R L and SCOTT J K Toxicity of inhaled ^{90}Sr in rats Hlth Phys 15 (1968) 173
17 WATANABE S Leucémies expérimentales provoquées chez la souris par administration répétée de petites doses de certains radioisotopes (^{32}P ^{89}Sr et ^{144}Ce) Pathologie Biologie (Extrait de la Semaine des Hopitaux) (1958) 34/23—24 1833—48
18 — Experimental studies on the development of leukemia in mice with frequent administration of small doses of some radioactive isotopes (^{32}P ^{89}Sr ^{144}Ce) September 1957

FROM THE MEDICAL SECTION OF THE STATE INSTITUTE OF RADIATION HYGIENE AND THE INSTITUTE OF GENERAL AND EXPERIMENTAL PATHOLOGY, UNIVERSITY OF OSLO, NORWAY

INTESTINAL CELL KINETICS IN IRRADIATED MICE

A quantitative investigation of the acute reaction to whole body roentgen irradiation

by

FINN DEVIK

Surgery still appears to be the only rational means of completely removing malignant body cells. Ionizing radiation, chemotherapeutic agents and hormones are to a considerable extent of an empiric character, although certain specific effects on cell metabolism, cell growth and growth regulation have helped to support such forms of therapy with some degree of success (STEINFIELD 1967). A suitable selective agent has, however, yet to be found.

Radiobiologic investigations have provided data on radiation effects in cells, e.g. morphologic and functional changes, depression of mitosis, chromosome breakage and cell death as an exponential function of dosage. The oxygen tension during radiation, effects on the nucleic acids and cellular mechanism for repair of injury are of fundamental importance. Research in radiobiology has, however, in the main not yet led to much change in established empiric radiotherapeutic practice. Cell population kinetics have assumed increasing importance in providing background material for a better understanding of homeostasis and growth as the balance between cell production and cell loss in the study of

Submitted for publication 11 December 1969.

the biology of tumours, (TUBIANA et coll 1968) LAMERTON & STEEL (1968) have recently reviewed the subject, and discussed the possibilities and limitations of the available methods

The epithelial cells in a crypt of the small intestine may be regarded as forming a well defined and delimited cell population Kinetic studies have provided much basic information, both under normal conditions and after injury, e g roentgen irradiation The general features of radiation effects have been known for many years Since REGAUD et coll (1912) called attention to gastrointestinal changes in dogs following irradiation, clinical morphologic, cytologic, biochemical and functional changes have been the subject of many publications (References appear in reviews by PIERCE (1948) and RUBIN & CASARETT (1968))

The principal events in the kinetics of the epithelial cells of the small intestine have for a long time been well understood from histopathologic and cytologic investigations Recently introduced techniques with labelling of cells have provided more details and led to quantitative determinations that were not previously possible In addition to cell counts, differential cell counts, mitotic index, abnormal mitoses, and number of dead cells, the duration of different phases of the cell cycle has been determined and the migration of cells from the crypts to the villi followed Most information has been obtained from mice and rats, but it would appear to be applicable in general to other species, including man

The cell population of an intestinal crypt is well suited for quantitative investigations The size, cell production and cell loss of a cell population of an intestinal crypt were therefore chosen for the present investigation on changes in the cell population to total destruction or elimination following an increasing degree of injury by roentgen irradiation

Material and Methods The experiments were performed with male and female albino mice of the WLO strain, 2 to 3 months old, weighing about 25 to 30 g and fed a standard diet of pellets and water ad libitum

Four mice at a time were given whole body roentgen irradiation in a plastic box, freely open to the surrounding air The integral dose was measured during each irradiation with a Philips dosemeter with the ionization chamber placed between the mice Two roentgen units had to be used, the *physical conditions* were as follows (1) 250 kV, 12 mA, filter 1 mm Cu, FSD 55 cm, dose rate 38 R/min The doses were 200 R (62 mice), 350 R (80 mice) and 700 R (120 mice) (2) 170 kV, 6 mA, filter HVL 0 85 mm Cu, FSD 28 cm, dose rate 140 R/min The doses were 700 R (36 mice) 900 R (8 mice), 1 000 R (54 mice), 1 200 R (8 mice), 1 400 R (30 mice), 1 700 R (8 mice) 2 000 R

(30 mice) and 2 400 R (12 mice) A further 156 mice were used to determine the LD o and study the migration of cells, and mitotic rates There were 47 control mice of the total of 651 mice

Of all the mice that received 700 R and more 126 were anesthetized during irradiation with subcutaneous injection of Nembutal (Abbot) *100 mg/kg body* weight, to permit comparison with localized irradiation in other experiments

The mice were killed by cervical luxation at time intervals as follows 1/2 1 2 3 4, 6 9 12 24 36 and 48 hours and 3, 4, 5, 6 and 7 days For several dose levels however mice were killed only at two or a few more time intervals

The material was fixed in Sanfelice s solution (16 parts CrO_3 1 % 1 part acetic acid and 8 parts formalin 40 % mixed shortly before use), embedded in paraplast sectioned serially at 5 μ and stained with hematoxylineosin Neutralized formalin 4 % was used for fixation for preparing autoradiographs of material labelled by intraperitoneal injection of tritiated thymidine (New England Nuclear Corporation thymidine methyl ^3H 10 Ci/mM 25 μCi per mouse) The slides for autoradiography were coated with Kodak NTB 2 emulsion, and following exposure and development were lightly stained with hematoxylin and eosin To determine mitotic rate 1 mg/kg body weight vinblastine sulfate (Velbe Lilly) was injected intraperitoneally (TANNOCK 1965) to arrest the mitoses counts were performed at the time of injection and 3 2/3 to 4 hours after injection

Counting Counts were made in transverse sections of the small intestine mid way between the doudenum and caecum where crypts sectioned longitudinally through the middle ten in each mouse were selected for analysis The cells counted were restricted to the cells cut through the middle part of the nucleus and lying in the same focal plane sections were obtained in series to minimize the effect of variation in thickness The results are given as number of cells mitoses dead cells and Paneth cells observed per section of one crypt

The epithelial cells of the villi have not been counted, since the number of cells counted in a section of a villus and a crypt cannot be directly compared to each other The crypts are more numerous than the villi and it is estimated that there are three to four crypts per villus in the parts examined although this varies very much in the sections as does the length of the villi

Epithelial cells of the crypts are usually easily distinguished from those of the villi the nucleus of the latter being more centrally located in the cell than in the former The counts of the total number of cells comprised mitoses and Paneth cells but did not include the dead cells

Variation in counts occurred both along the small intestine, and between

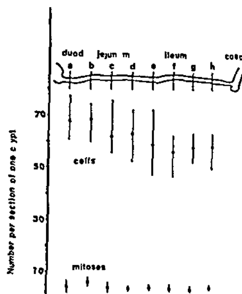


Fig 1 Number of cells per crypt section along the small intestine at 8 places spaced at equal intervals between the stomach and the caecum The vertical bars indicate the range of the mean values obtained from 6 mice

individual mice Fig 1 gives the results of counts of the number of epithelial cells per section of a crypt from eight different parts along the small intestine in 6 control mice The decrease in number of cells per section towards the aboral part is gradual and in no place abrupt The exact location from where the specimen is taken is therefore not critical The mean value ± 1 SD of cell counts from mid way between the duodenum and caecum in 42 control mice was 57 6 ± 7 5

Record was made of those crypts in a transverse section of the intestine that demonstrated the basal part of the lumen to obtain data on the relative changes in the cell population of the whole intestine Since this number would depend on the diameter of the lumen, considerable variations were expected In the preparations with the most marked changes this estimate was considered to be better than counting all the crypts

The mitotic counts included the stages from prophase to early telophase, when the nuclear membrane was absent Mitoses normally exhibited considerable diurnal variations with peak values in the afternoon and early morning in these mice The mice were irradiated and sacrificed at different times of the day, but it was considered that corrections for diurnal variations in the irradiated mice were not necessary and would introduce an unnecessary complicating factor The mean number ± 1 SD was 3 7 ± 1 9 mitoses per section of one crypt in 47 control mice

The more central location towards the axis of the crypt of mitoses of many of the dead cells as well as of the Paneth cells, implies that counts performed

in sections represent and overestimate of their frequency relative to the other cells TANNOCK (1965) estimated the true value for mitoses to be about 57 % of the counts observed in normal mice Such corrections have not been made, however because the factor obviously varies with the radiation reaction in the crypts, and in the case of Velbe administration numerous mitoses also occurred towards the periphery of the crypts

Dead cells were easily identified by their eosinophilic or lysed cytoplasm and pyknotic or fragmented nuclei with dense staining and loss of granulated structure some of them were encountered in the lumen of the crypt When dead cells were numerous the exact number per sectioned crypt was difficult to assess because of the fragmentation of the nuclei In sections from normal mice the number of dead cells varied considerably, the mean value ± 1 SD from 47 mice being 0 83 ± 0 85, the median value was 0 5, and two thirds of the values were between 0 3 and 1 2 per section of one crypt

The Paneth cells with their granulated cytoplasm in the bottom of the crypt were in most sections easily distinguished from the other cells The mean number per section ± 1 SD was 6 1 ± 1 5

Goblet cells and argentaffine cells have not been recorded separately in the present work

The counts were made by a trained assistant without knowledge of radiation dose and time intervals of the specimens To test the reliability of the counting procedure the assistant was asked to count again 11 slides she had counted seven months previously without knowing the identity of the slides. The average of the first counts was 47 3 cells per crypt section and on the second 48 4 and in no single slide was the deviation between the two values more than 7 3 % per crypt section

Effect of narcosis Since some of the mice were anesthetized during irradiation it must be pointed out that anesthetics and narcotics may afford a slight protection to whole body irradiated animals (COTTIER 1966) probably due to induced hypoxia although increase in mortality has also been reported (ZAUDER 1959) The Nembutal narcosis was not deep enough to cause cyanosis which is easily observed in experiments with hypoxia in albino mice Pilot experiments with 45 mice revealed no clear difference in radiation lethality between anesthetized and non anesthetized mice (the quotients indicate the mice surviving 30 days/mice irradiated)

Doses	600 R	700 R	800 R
Anesthetized mice	4/7	1/8	0/7
Non anesthetized mice	3/8	1/8	1/7

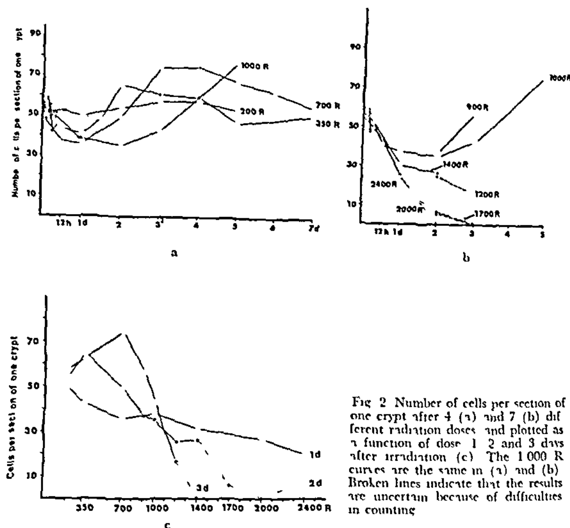


Fig 2 Number of cells per section of one crypt after 4 (a) and 7 (b) different radiation doses and plotted as a function of dose 1 2 and 3 days after irradiation (c) The 1 000 R curves are the same in (a) and (b) Broken lines indicate that the results are uncertain because of difficulties in counting

Furthermore, differences in cell counts between such groups have not been significant A possible effect of narcosis is therefore considered to be slight enough to be disregarded in these experiments, and the results from anesthetized and non anesthetized mice have been pooled

Results

Most points on the curves represent the arithmetic mean values from 4 mice, in some cases 6 or more, and in a few instances 2 mice Comparison between results obtained at different doses and time intervals should ideally be made in mice from the same batches in experiments done at the same time, but for practical reasons it has been necessary to perform a number of smaller series

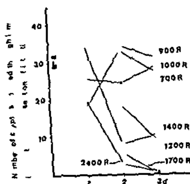


Fig 3 Relative number of crypts in a transverse section of the intestin The points close to the ordinate illustrate the distribution in normal mice

of separate experiments It has been found justifiable to pool the results since they are coherent and well reproducible

The number of crypt cells is given in Fig 2, a and b With doses above 200 R there is a reduction in cell number during the first day followed by an increase after two days in the 350 and 700 R eries and after three days in the 900 and 1 000 R series The increase continues to values *higher than* normal after 350, 700 and especially after 1 000 R After 1 200 and higher doses the initial decrease continues during the three days of observation, approaching zero values for doses of 1 400 R and above

The data may be plotted in a different way as in Fig 2c with dose instead of *time along* the abscissa and each curve referring to a given time interval instead of a *dose It is seen how* the decreased number of cells the first day does not change much with increasing dose A compensatory increase is indicated on the second day following low doses the increase becoming marked on the third day *and after higher doses* when the values on this day decrease steeply towards zero around 1 400 R It should be noted that counting of cells was difficult in sections with marked radiation changes and that the very low counts are indications rather than accurate figures

The *relative* number of crypts did not decrease below normal after doses of 700 900 and 1 000 R (*Fig* 3) A decrease was observed after 1 200 R and higher doses This did not become apparent until the second day and was considerable on the third day when, following 1 700 and 2 400 R crypts were almo t absent

The results of mitotic counts per crypt after seven dose levels are given in Fig 4 The well known initial depression has not been detailed Except for the highest dose levels, an increase may be noted after two days, and maximum counts are recorded on the third day thereafter the number decreases

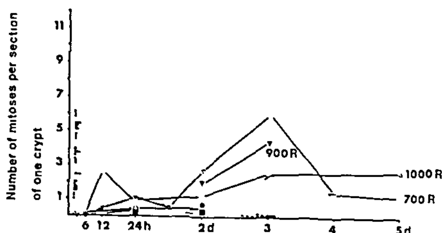


Fig 4 Number of mitoses per section of one crypt The points close to the ordinate illustrate the distribution in normal mice Broken lines indicate that the results are uncertain because of difficulties in counting

Since mitotic counts do not give information on the rate of cell production unless the mitotic duration is known, vinblastine was injected to stop mitoses, and arrested mitoses were counted at four hours, on the first, second and third days after 1 000 R The results are given in Table 1 The mitotic rate has in this case been calculated by the formula

$$\frac{M_T - M_0}{T} = \text{number of mitoses per hour,}$$

where M_0 and M_T are the mitotic index before injection of vinblastine and after T hours To be valid the method, inter alia requires steady state conditions, and since in this instance the conditions at best may be considered only as an approximation, *the figures in Table 2 must be evaluated with reserve*

The number of dead cells observed after six dose levels are given in Fig 5 About three hours after irradiation, there is a marked peak increasing in size with dose, the numbers then gradually return to near normal values The dead cells are most abundant in the lower part of the crypts, their distribution being very similar to the distribution of mitoses The dead cells are also frequent in the Paneth cell region

The number of Paneth cells (Fig 6) seems to be influenced relatively little by the radiation as long as there is no marked decrease in cell number If so, they also disappear, depopulated crypts with only Paneth cells left were not observed

In the overall cell population kinetics of the crypts the drain of cells to the villi is important, and may be studied by following the migration of labelled

Table 1

Estimated mitotic rate duration of mitosis and mean generation time 1 2 and 3 days after 1 000 R — The figures represent average values from 4 mice

	Controls	1 day	2 days	3 days
Befo e I elbe inject on				
M toses per crypt section	1 5	1 0	0 5	1 6
Cells per crypt sect on	58 6	33 5	29 8	38
Mitotic ndex $M_0 \frac{\text{mitoses}}{100 \text{ cells}}$	2 56	3 0	1 7	4 2
Int rval T	3 2/3 h	4 h	4 h	4 h
Afte I lbe i j ction				
M toses per crypt section	6 1	1 7	3 8	14 2
Cells per crypt section	60 2	28 6	3? 0	43 9
Mitotic index $M_T \frac{\text{mitoses}}{100 \text{ cells}}$	10 1	6 2	11 9	32 3
M tot c rate mitoses per hour per 100 cells	2 1	0 8	2 6	7 0
Duration of m tosis $\approx \frac{\text{mitot ndex}}{\text{mitotic rate}}$	1 25 h	3 75 h	0 67 h	0 6 h
Mean generation time $\approx \frac{1}{\text{m tot c rate}}$	48 h	125 h	39 h	14 2 h

cells Fig 7 indicates that for two days there was little difference between the migration in the normal intestine and after radiation with doses of 700 and 2 000 R The distance of migration recorded was from the base of the villus to the most advanced of the labelled cells on the villus The changes seen in sections of the mall intestine up to five days after 1 000 R are illustrated in Fig 8

Discussion

A full account of the population kinetics of the irradiated epithelial cells in the small intestine is a complex task because of the great variability in size, shape and number of villi Since it is usually easy to distinguish between cells in crypts and cells on villi the present study has limited the quantitative in vestigations to the cells in the crypts these have tentatively been regarded as a closed population in which it is possible to characterize quantitatively several

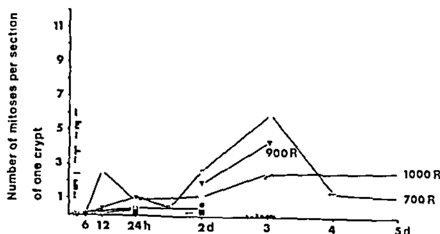


Fig 4 Number of mitoses per section of one crypt The points close to the ordinate illustrate the distribution in normal mice Broken lines indicate that the results are uncertain because of difficulties in counting

Since mitotic counts do not give information on the rate of cell production unless the mitotic duration is known, vinblastine was injected to stop mitoses, and arrested mitoses were counted at four hours, on the first, second and third days after 1 000 R The results are given in Table 1 The mitotic rate has in this case been calculated by the formula

$$\frac{M_T - M_0}{T} = \text{number of mitoses per hour,}$$

where M_0 and M_T are the mitotic index before injection of vinblastine and after T hours To be valid the method, inter alia requires steady state conditions, and since in this instance the conditions at best may be considered only as an approximation, the figures in Table 2 must be evaluated with reserve

The number of dead cells observed after six dose levels are given in Fig 5 About three hours after irradiation, there is a marked peak increasing in size with dose, the numbers then gradually return to near normal values The dead cells are most abundant in the lower part of the crypts, their distribution being very similar to the distribution of mitoses The dead cells are also frequent in the Paneth cell region

The number of Paneth cells (Fig 6) seems to be influenced relatively little by the radiation as long as there is no marked decrease in cell number If so, they also disappear, depopulated crypts with only Paneth cells left were not observed

In the overall cell population kinetics of the crypts the drain of cells to the villi is important, and may be studied by following the migration of labelled

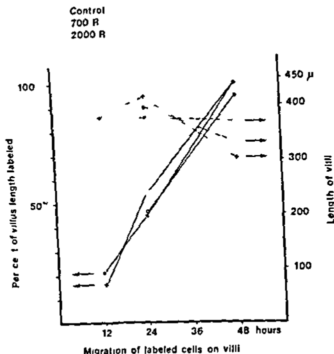


Fig 7 Migration of labelled cells along villi Fully drawn lines refer to the ordinate to the left which indicates the percentage of length of villi and broken lines refer to the ordinate to the right which gives the length of the villi observed

Abnormal mitoses with chromosome aberrations are conspicuous when cell divisions begin again after the mitotic depression but their relative number decreases rapidly, and two days after 700 R most of the mitoses in the crypts have normal appearances (DEVIK 1968)

Regarding the dead cells with pyknotic nuclei it is interesting to see the abrupt increase in their number about two hours after irradiation at all dose levels with a maximum at about three hours The maximum apparently correlates with dose in spite of the counting difficulties when many dead cells are present The value of the maximum as a possible indicator of radiation dose is limited however by the narrowness of the peak on the time scale It is not known how long the dead cells remain in the crypts after they can be recognized as dead The steep falling part of the curves indicate that this clearance time is of the order of a few hours or even less for many of them, others may remain for several hours

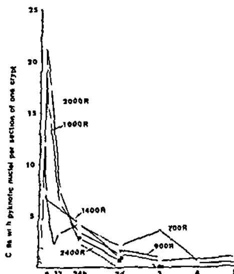


Fig 5 Number of dead cells recorded per section of one crypt Broken lines indicate that the results are uncertain because of difficulties in counting

main parameters of population kinetics The number of cells on the villi and the total life span of the epithelial cells have been determined It should also be mentioned that characteristics of crypt cells under abnormal conditions may be found on villi, e g cell divisions, but this has only been observed occasionally in the present experiments when extreme changes existed The present results are in accordance with previously published information on radiation effects in the intestines, where such information is available

The immediate and strong influence on the number of dividing cells corresponds closely to the detailed data from the rat published by Williams et coll (1958) A temporary and compensatory 'overshoot' of mitoses is observed after doses that are not too high For cells in vitro (Elkind et coll 1963) mitoses disappear for a time where the number of hours is about the same as the dose expressed in hundreds of rad (e g four hours following 400 rad), and a similar relationship seems to apply to the mitoses in the crypts of the mouse

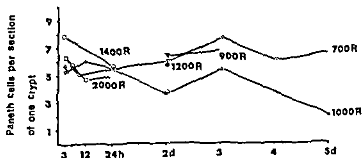


Fig 6 Number of Paneth cells per section of one crypt Broken line indicates that the result is uncertain because of difficulties in counting

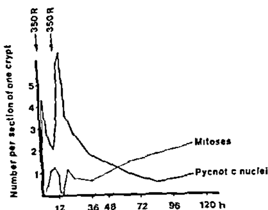


Fig 9 Inverse relationship of mitoses and dead cells after two doses of 350 R spaced 12 hours apart

& LOTHE 1955) This mode of cell death thus occurs in other tissues as well although it is usually less conspicuous

Lymphocytes are known to be very sensitive to irradiation, as well as to many other types of injury or influences and extensive degeneration of these cells may be demonstrated after a short time Since lymphocytes are highly differentiated cells they are generally regarded as an exception to BERGONIE TRIBONDEAU'S law (1906) However it is known that lymphocytes may be induced to divide at short notice and with the relationship between pyknosis and mitosis in the crypts in mind it is possible that radiation induced degeneration of lymphocytes may be connected with a preparedness for mitosis This might be a confirmation of rather than a contradiction to the law

As a result of cell death, depression of mitoses and migration of cells to the villi the number of cells in the crypts is rapidly reduced until cell production is again restored

A repopulation of the crypts to cell numbers above the normal after the temporary depression occurs after 1 000 R 700 R 350 R, and may be indicated after 200 R LESHER (1968) has pointed out that there may be a marked overshoot after 1 000 R The results indicate that in these mice the epithelial cells in the crypts can survive and regenerate after lethal doses of whole body irradiation, at least up to 1 000 R When the dose is increased to 1 200 R 1 400 R and more depopulation of the crypts becomes marked in the course of two to three days and regeneration is not apparent in histologic sections before the mice die A dose of about 1 200 R seems to be a critical level with respect to intestinal death of the mice After a single local irradiation of the intestine regeneration of epithelial cells in the crypts may take place after doses approaching 2 000 R (WITHERS & ELKIND 1968)

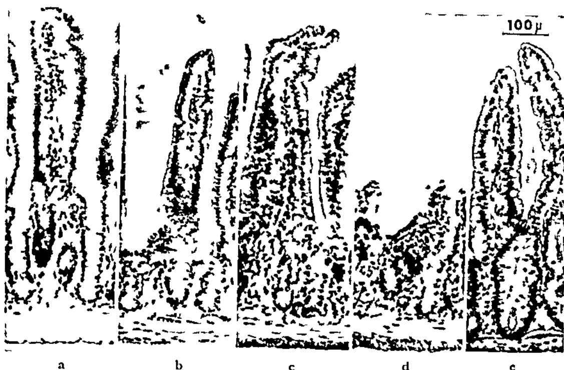


Fig 8 Changes in the small intestine after 1 000 R whole body irradiation a) Control b) c) and d) The crypts present marked changes 1 2 and 3 days respectively after irradiation The villi are little different from normal after 1 and 2 days but on the 3rd day their size is greatly reduced e) Regeneration of villi and crypts is almost complete by the 5th day

The cells that become pyknotic after irradiation seem to have been in a state closely or directly related to the processes preparatory to mitosis A great part of the pyknotic nuclei are labelled when tritiated thymidine is injected before irradiation (SHERMAN & QUASTLER 1960, DEVIK 1968) When the label was injected five hours before a dose of 350 R, 68 % of the pyknotic nuclei were found to be labelled two hours later These cells had been in the S phase at the time of labelling, but died before entering mitosis The curves in Fig 5 clearly demonstrate that cell death may be frequent before the mitotic activity is resumed

A connection between early pyknosis and mitosis is also indicated by the inverse relationship of the number of cells acutely destroyed and the number of mitoses (WILLIAMS et coll), particularly after relatively low doses (DEVIK) It is illustrated in Fig 9 with curves from a set of experiments with split doses, 350 R was given twice with an interval of twelve hours

In connection with the post irradiation pyknosis in the crypts, a similar, though less marked appearance of degenerate cells was noted in bone marrow squash from mice, between two and six hours after irradiation with 200 R (DEVIK

Fig. 10. Extrapolation of the cell survival curve of WITHERS & ELKIND (rectangle to the right).

Discussion

The technique used by WITHERS & ELKIND is restricted to relatively high doses and to that part of the exponential curve where relatively few nodules representing single surviving cells can be counted: it would hardly be possible to make counts after doses that left survivors in every crypt. With this reservation an extension of their dose survival curve has been plotted in Fig. 10. The lower end seems well established; the upper part must terminate at the number of cells exposed to irradiation and at dose 0. The total irradiated population of crypt cells in their experiments can be estimated to have been about 3×10^7, a figure that the present author considers unlikely to be wrong by more than a factor of 2 either way. (About 20 mm intestine was irradiated. It is assumed that with an average diameter of 50 μ there are 400 crypts along 20 mm, that there are 150 crypts per transverse section of the intestine and that each crypt contains 500 cells.)

Cells may die in ways other than passing through a stage recognized as pyknosis, e g by lysis, which is not so easily followed in the microscope Abnormal cells produced by abnormal mitoses may suffer a delayed death However, it appears that the early reduction in the number of cells in the irradiated crypts may mainly be accounted for by the pyknotic cells, apart from migration

The number of cells per section of one crypt may be taken as a good relative indicator of the total number of cells in the crypt as long as the conditions are not much different from normal When the number per longitudinal section is reduced, however, the number per transverse section will also be reduced, most likely by a similar factor The total number of cells in a crypt will therefore represent a greater reduction than indicated by the cell counts in the curves in Fig 2, a and b A reduction in the number of crypts makes the difference still more obvious (Fig 3) Cell counts in the transverse sections were made after 1 000 R to calculate approximately the total number of cells in a crypt The results are given in Table 2 The present results are in good agreement with results obtained by KONONENKO (1968) in mice irradiated with 700, 900 and 1 200 R

Two to three days after high doses, morphologic changes of the cells left in the crypts may be marked with increase in size, bizarre forms with nuclear irregularities, and changes in stainability A reduction in size of the villi after a few days takes place when the cell production is severely restricted and there are not enough cells to meet the demand for migration In view of the profound radiation effects in the crypts, it is somewhat surprising to find that migration of cells from the crypts to the villi is at first little affected even by considerable doses of radiation, i e up to 3 000 rad (HUGHES et coll 1958, SHERMAN et coll 1958) (cf also Fig 7)

Investigations of functional changes in the intestines after irradiation are less numerous than morphologic studies Reviews have been published by BOND (1963) and BOUCKAERT (1968) Differentiation between effects on epithelial cells of villi or crypts cannot usually be made in investigations of functional changes

The radiation response of the small intestine in terms of cell survival data may be considered with the present results

An exponential dose survival curve in cell cultures may be demonstrated for many cell types, and the D_0 or D_{37} (the dose that reduces the number of cells capable of proliferation to 37 %) has usually been stated to be around 100 R WITHERS & ELKIND (1968) reported an exponential function with a D_0 of 100 R for epithelial cells in the intestinal crypts of mice in experiments performed with local irradiation in vivo Their data will be used in the following discussion

Table 2

Estimated total number of cells per crypt following 1 000 R — Each figure represents four mice

	Controls	1 day	2 days	3 days	5 days
Cells per longitudinal section of one crypt (a)	58 6	38 0	35 3	40 7	77 7
Cells per transverse section of one crypt (b)	19 5	10 2	10 4	11 3	19 5
Total number of cells *per crypt* $\frac{(a)}{2} x$ (b)	571	194	18[illegible]	230	757

700 and 2 000 R and therefore presumably also following 1 000 R However since a normal rate of migration means a daily cell production of the same order as the normal crypt population, and since the cell production is much decreased during the first two days the true rate must be lower A moderate re arrangement of the anatomic form of the villi may greatly affect the surface of the villi as pointed out by CREAMER (1964), and it is likely that a reduction takes place One day after 1 000 R the cell number observed is still about a third of the normal whereas the *surviving cells* are expected to constitute only 1 2 % of the normal or 3 % of the actual population at this time The rest of the cells are supposed to be non viable and a further rapid decrease towards a still slowly rising hypothetic curve would be expected A decrease would also be likely because migration still goes on along the villi (cf Fig 7) and presumably al o out of the crypts

This initial discrepancy between the observed and the hypothetic number of cells becomes less marked when relevant modifying factors are taken into account

1 If lethally injured cells were able to divide one or several times before they succumb a fall in the number of cells would be counteracted Abnormal cell divisions in the crypts produce abnormal cells many of which may be recognized by nuclear abnormalities fragmented nuclei and micronuclei Such cells are found in the crypts one two and three days after 1 000 R Some of them may lie at the base of the villi after one day and a little higher after two days when most of the cell on the villi appear normal After three days when the villi are hrunken their epithelium is abnormal and many cells have fragmented nuclei and micronuclei indicating that by now the normal appearing cells have been shed and replaced with what is available of abnormal cell off pring The presence of such cells indicates that they are at least a contributing factor to explain the discrepancy

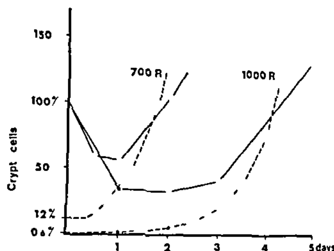


Fig 11 Cell numbers in crypts after 700 and 1 000 R as percentages of normal values (full lines) and hypothetic repopulation in crypts (broken lines)

The experimental results after 700 R and 1 000 R are compared in Fig 11 to hypothetic curves derived from the cell survival curve of WITHERS & ELKIND The numbers of cells following 1 000 R are as in Table 2 The figures for 700 R have been calculated by assuming that transverse sections of the crypts had the same relative change in number of cells as the longitudinal sections The hypothetic curves have been constructed as follows The theoretic number of surviving cells following 1 000 and 700 R is estimated to be 0 6 and 12 % respectively (Fig 10) It is assumed that following 1 000 R the surviving cells divide once in the first 24 hours, and thereafter every 12th hour Seven cell divisions in the course of 4 days would bring the number of cells to the level observed The fact that the cell cycle may be even shorter than 12 hours, when the repopulation begins, has been ignored LESHER & BAUMAN (1969) reported a cell cycle time of less than 7 hours at three days after 1 000 R determined by counting the labelled mitoses After 700 R the first division is assumed to take place within 18 hours and thereafter every 12th hour Three cell divisions in the course of 2 days would bring the number of cells to the level observed

There is an apparent discrepancy between hypothetic and experimental curves in their earlier parts The degree of depopulation of cells in the crypts after irradiation is much less than expected, even after 1 000 R, if it is assumed that the lethally injured cells disappear and only the proliferating ones remain The initial degree of cell depletion does not present great variation within the dose range 350 to 1 000 R (Fig 2a), the cell number alone would not be a good indicator of dose

The migration of labelled cells along the villi seems to indicate that the migration rate is not much different from the normal for two days both after

estimated that two thirds of the cells would survive a dose of 350 R and practically all cells a dose of 200 R The experimental data (Fig 2a) seem to agree fairly well with this Available experimental evidence therefore appears to agree that an exponential cell survival curve of the crypts has a high extra polation number, perhaps of the order of 100

The ability of the intestinal epithelium for repair and regeneration is also well illustrated by LAMERTON's report on experiments with continuous irradiation of rats (1966) in which he called attention to the 'remarkable capacity for recovery of normal crypt population even after a total accumulated dose of about 2 000 rad in 5 days

The quantitative determination of cellular changes in a closed cell population after irradiation provides information of general interest, both with respect to time and mode of death of cells cell production, cell migration, size of cell population and regarding the extrapolation number N and the D_0 If radiobiology is going to provide a better theoretic background for radiotherapy, it is especially important to know the latter parameters for as many cell types as possible It seems likely that an analysis of the crypt cell population may also provide information of value with respect to the mode of action of drugs and cytotoxic agents.

The quantitative data mainly provide an illustration of injury suffered by actively dividing cells which constitute the majority of the cells of the crypts The Paneth cells are differentiated cells which in part consist of cells that either have a long generation cycle or that no longer divide (DEVIK & IVERSEN 1970) Their number is found to be little affected during the first days after irradiation but they disappear when the number of cells in the crypts is much decreased The results indicate that the Paneth cells either are destroyed by irradiation in the course of a few days when the dose is high enough around 1 200 R or that their existence depends upon the presence of the other epithelial crypt cells

Acknowledgements

The author wishes to thank the Norwegian Defence Research Establishment for providing facilities and assistance during the preliminary phases of the work He is grateful to Mrs M Halvorsen for valuable technical assistance and counting and for the preparation of the illustrations together with Mrs H Anundsen

SUMMARY

Quantitative estimates were made of the number of epithelial cells mitoses dead cells and Paneth cells in the intestinal crypts of mice following increasing doses of whole body

2 Lethally injured cells may stay alive for some time and prevent a further depletion in the number of cells until regeneration is well established It seems likely that this factor is of significance

3 Repair of lethally injured cells in addition to repair expressed by the 'shoulder' of the exponential curve could take place at these dose levels It may be that this factor is significant It is not possible at present to decide which of these three factors is more important, but it is considered likely that together they may account for the values observed

4 Substitution of cells by migration from outside could also be mentioned but this possibility is considered so unlikely as to be disregarded

When regeneration starts and the number of cells again increases, the time for the increase observed seems to coincide closely with the hypothetic increase, which therefore could account for this part of the curves It may be concluded that the experimental results are compatible with an exponential cell survival curve, as illustrated in Fig 10 It would however be difficult to postulate compatibility if the curve had a course that gave markedly fewer survivors than the 0 6 % and 12 % as indicated for the two higher dose levels

The suggested extrapolation of the curve is also in agreement with the observations on the numbers of crypts Allowing for considerable variability of this parameter, it is evident from Fig 3 that it is hardly affected by doses up to and including 1 000 R A decrease is observed with doses of 1 200 R and more Assuming that one intact cell is enough to repopulate a crypt (which has a population of about 500 cells), a reduction in the number of crypts would be expected when the probability for survival is less than 1 500 This value on the exponential curve corresponds to 1 000 rad or 1 060 R which is rather close to the dose level at which the number of crypts becomes reduced

The extrapolated curve in Fig 10 indicates an extrapolation number of the order of 100, which is a high value for such a figure A lower extrapolation number would be obtained if the number of cells had been much underestimated, or if the slope of the curve were less steep Since all the cells in the crypts are regarded here as potentially dividing stem cells the number of cells seems to be overestimated rather than underestimated Any significant change in the slope would mean a considerable departure from the data obtained by WITHERS & ELKIND

A high extrapolation number suggests a high degree of ability of the cells to repair injury Based on data from irradiation with split doses, WITHERS & ELKIND described a recovery factor of about 60 at 24 hours after 700 R On the basis of split dose experiments, HORNSEY & VATISTAS (1963) also suggested a high degree of recovery, with an extrapolation number of more than 28, assuming a D_0 of 120 R From the hypothetic curve in Fig 10 it may be

HORNSEY S and VATISTAS S Some characteristics of the survival curve of crypt cells of the small intestine of the mouse deduced after whole body X irradiation Brit J Radiol 36 (1963) 795

HUGHES W L BOND V P BRECHER G et coll Cellular proliferation in the mouse as revealed by autoradiography with tritiated thymidine Proc nat Acad Sci 44 (1958) 476

KONONENKO A M Some characteristics of the crypt cell population kinetics in normal and irradiated small intestine of the mouse Citologia 10 (1968) 1410

LAMERTON L F Cell proliferation under continuous irradiation Radiat Res 27 (1966) 119

— and STEEL G G Cell population kinetics in normal and malignant tissues *In* Progress in biophysics and molecular biology Edited by J A V Butler and D Noble Pergamon Press Oxford 1968

LESHER S and BAUMAN J Recovery of reproductive activity and the maintenance of structural integrity in the intestinal epithelium of the mouse after single dose whole body ^{60}Co γ ray exposures *In* Effects of radiation on cellular proliferation and differentiation p 507 International Atomic Energy Agency Vienna 1968

— — Cell kinetic studies of the intestinal epithelium Maintenance of the intestinal epithelium in normal and irradiated animals *In* Human tumor cell kinetics Nat Cancer Inst Monogr 30 (1969) 185

PIERCE M The gastrointestinal tract *In* Histopathology of irradiation from external and internal sources p 507 McGraw Hill New York 1948

REGAUD C NOGIER T et LACASSAGNE A. Sur les effets redoutables des irradiations étendues de l abdomen et sur les lésions du tube digestif déterminées par les rayons de roentgen Arch Élect méd 21 (1912) 321

RUBIN Ph and CASARETT G W Clinical radiation pathology p 194 Saunders Philadelphia 1968

SHERMAN F G and QUASTLER H DNA synthesis in irradiated intestinal epithelium Exp Cell Res 19 (1960) 343

— BRECHER G CRONKITE E P and QUASTLER H DNA synthesis cell duplication and migration in the small intestine of normal and irradiated mice Fed Proc 11 (1958) 148

STEINFIELD J L The chemical treatment of advanced cancer in man Nat Cancer Inst Monogr 24 (1967) 271

TANNOCK I F A comparison of the relative efficiencies of various metaphase arrest agents Exp Cell Res 47 (1965) 345

TUBIANA M FRINDEL E et MALAISE E. La cinétique de prolifération cellulaire dans les tumeurs animales et humaines — influence d une irradiation *In* Effects of radiation on cellular proliferation and differentiation p 423 International Atomic Energy Agency Vienna 1968

WILLIAMS JR R B TOAL J N WHITE J and CARPENTER H M Effect of total body X radiation from near threshold to tissue lethal doses on small bowel epithelium of the rat I Changes in morphology and rate of cell division in relation to time and dose J nat Cancer Inst 21 (1958) 17

WITHERS H R and ELKIND M M Dose survival characteristics of epithelial cells of mouse intestinal mucosa Radiology 91 (1968) 998

ZAUDER H L Response of radiated animals to anesthetics and analgetics Abstract Reference No 5683 *In* The effects of radiation and radioisotopes on the life processes TID — 3098 US Atomic Energy Commission Division of Technical Information Washington 1963

roentgen irradiation at intervals of up to seven days The results are compatible with an *exponential cell survival curve with a high* extrapolation number The crypt cell population may prove useful in investigating reactions of rapidly proliferating cell populations to various external influences

ZUSAMMENFASSUNG

Es wurde die *Zahl* der epithelialen *Zellen* der Mitosen, der toten Zellen und der Paneth Zellen in den Darmkrypten von Mausen nach steigenden Dosen von Ganzkorper Rontgen bestrahlung in Intervallen bis zu sieben Tagen bestimmt Die Resultate lassen sich mit einer exponentiellen Zell Überlebenskurve mit einer hohen Extrapolationszahl vereinen Die Population der Krypten mag bei Untersuchungen der Reaktionen einer rasch proliferierenden Zell population unter verschiedenen ausseren Einflussen anwendbar sein

RÉSUMÉ

L auteur a fait des estimations quantitatives du nombre de cellules épithéliales de mitoses de cellules mortes et de cellules de Paneth dans les cryptes intestinales de souris apres des doses croissantes d irradiation totale du corps par les rayons de roentgen a des intervalles allant jusqu à sept jours Les resultats sont compatibles avec une courbe exponentielle de survie des cellules avec un nombre d extrapolation eleve La population de cellules des cryptes peut se montrer utile dans l etude des reactions de population cellulaire à proli feration rapide soumise à differentes influences externes

REFERENCES

BERGONIÉ J TRIBONDEAU L et D ARSONVAL M Interprétation de quelques résultats de la radiothérapie et essai de fixation d une technique rationelle C R Acad Sci 143 (1906) 983

BOND V P Effects of radiation on intestinal absorption Amer J clin Nutr 12 (1963) 194

BOUCKAERT A Les troubles du métabolisme des électrolytes dans le radiosyndrome intestinal J belge Radiol 51 (1968), 89

COTTIER H Histopathologie der Wirkung ionisierender Strahlen auf höhere Organismen (Tier und Mensch) *In* Handbuch der medizinischen Radiologie II/2 S 64 Springer Verlag Berlin New York 1966

CREAMER B Variations in small intestinal villous shape and mucosal dynamics Brit med J (1964) II p 1371

DEVIK F Quantitative cellular aspects of the epithelium in the small intestine of mice following total body irradiation Cell death mitosis and chromosome aberrations *In* Effects of radiation on cellular proliferation and differentiation p 531 International Atomic Energy Agency Vienna 1968

— and IVERSEN O H Observations on the generation time of Paneth cells in mice Virchows Arch Abt B Zellpath 4 (1970) 191

— and LOTHE F The effect of cysteamine cystamine and hypoxia on mortality and bone marrow chromosome aberrations in mice after total body roentgen irradiation Acta radiol 44 (1955) 243

ELKIND M M HAN A and VOLZ K W Radiation response of mammalian cells grown in culture IV Dose dependence of division delay and postirradiation growth of surviving and non surviving Chinese hamster cells J nat Cancer Inst 30 (1963) 705

has been reported in which abscopal damage has been initiated by damage to the anterior portion of an animal or by damage to any tissue other than the gastro-intestinal tract

Because of the importance of the lymphatic organs of the chicken in studies of immune processes (GOOD et coll 1966) and because their anatomic position offers distinct advantages for these types of studies the relative importance of direct cell killing (scopal damage) and abscopal damage in the radiation induced involution of the lymphatic tissues of the chicken have been examined In the chicken the thymus is located in the neck forming 8 lobes along each jugular vein A second large lymphoepithelial organ the bursa of Fabricius is located posteriorly dorsal to the cloaca These lymphatic organs have been shown to be radiosensitive (MONTOUR 1968), decreasing in weight proportional to roentgen dose between 50 R and 400 R Because of their anatomic positions it was possible with shielding to deliver a roentgen dose to a large portion of the animal, either anterior or posterior with negligible scattered radiation to the particular lymphatic organ under the shield It was thus possible to determine whether or not abscopal damage played a role in the involution of the chick lymphoepithelial organs following sublethal radiation exposure the extent of its contribution and whether or not such an effect occurred only following exposure of the gastro intestinal tract

Materials and Methods

Exposure conditions The source of radiation was a conventional therapy roentgenray machine operated at 250 kVp and 15 mA with 0 5 mm Al and 1 0 mm Cu added filtration The dose rate, measured at 71 cm TSD with a commercially calibrated Victoreen R meter under conditions of maximum backscatter was 58 6 R/min Doses of O R 200 R 400 R or 600 R were delivered to the anterior half of the body the posterior half of the body or to the whole body The exposure setup is illustrated in Fig 1 In this arrangement the thymus or bursa was in approximately the same position within its quadrant of the exposure area regardless of which of the three exposures was being performed Exposure positions were systematically altered throughout although the measured dose varied by less than 4 % from the midpoint of the 8 inch (20 3 cm) exposure square to the edge of the shield in any direction The variation in dose at the mid points of the four quadrants was less than 1 % Shielded lymphatic organs were from 8 to 10 cm from the edge of the shield Under the shield the dose was reduced to less than 10 % at 1 cm less than 5 % at 3 cm and less than 1 % at 8 cm

Animals A total of 240 single comb white leghorn cockerels obtained from

DIVISION OF RADIATION BIOLOGY, DEPARTMENT OF RADIOLOGY, VIRGINIA COMMONWEALTH UNIVERSITY, MEDICAL COLLEGE OF VIRGINIA, RICHMOND, VIRGINIA, USA

ABSCOPAL RADIATION DAMAGE TO CHICK THYMUS AND BURSA OF FABRICIUS

by

JAMES L MONTOUR

Thymic atrophy in mammals following whole body irradiation is probably the net result of both direct (scopal) and indirect (abscopal) damage LEBLOND & SEGAL (1942) observed a decrease in thymic weight 48 hours after abdominal irradiation with 2 000 R or 5 000 R CORP et coll (1961) performed similar experiments and concluded that these results could be explained on the basis of scattered rediation reaching the thymus BOND et coll (1953) using a deuteron beam which produced no significant lateral scattering demonstrated that irradiation of the gut with 3 564 rad of deuterons produced a significant decrease in thymic weight and increase in adrenal weight 6 days after exposure These findings are consistant with adrenal pituitary involvement subsequent to severe injury to the gastro intestinal tract, that is, the general adaptation syndrome of SELYE (1950) LAW & MOLE (1961) also found an abscopal effect on the rat thymus which they stated was not dependent upon the presence of the adrenals but related to food intake In all of the above experiments, damage to the gastro-intestinal tract has been implicated whether the abscopal damage has been associated with adrenal activity or with reduced food intake alone No experiment

Submitted for publication 11 July 1969

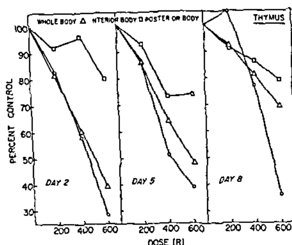


Fig. 2. Thymic weights following whole body, anterior body or posterior body irradiation.

Results

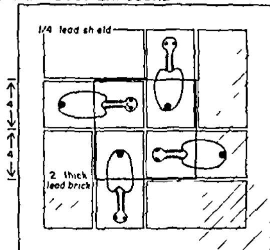
Thymic response (Fig. 2). Posterior body exposure resulted in a decrease in thymic weight compared to control weights at all dose levels measured 2 days post exposure. At 400 R and 600 R the decrease in thymic weight was maximum on the fifth day post exposure while weight loss was similar on each day after 200 R.

The two-day thymic weight dose responses were approximately linear for both whole body and anterior body irradiation with ED_{50} (50 % depression) values of 450 to 500 R. The 200 R and 400 R weights were not different in the groups but at 600 R the average weight of the whole body group was significantly less than that of the anterior body group ($p < 0.5$). Five days post exposure, the weights were similarly different at 600 R ($p < 0.05$) and at 400 R as well ($p < 0.05$). The five day ED_{50} values were 425 (whole body exposure) and 575 R (anterior body exposure).

Eight days post exposure two differences were apparent between the whole body and anterior body groups. The average thymic weight of the whole body and anterior body group was larger at 200 R ($p < 0.05$) and the average thymic weight of the anterior body group was considerably larger at 600 R ($p < 0.01$) than that of the whole body group. The difference noted at 200 R was contradictory to the generally observed equal or greater depression of lymphatic tissue due to whole body irradiation compared to partial body irradiation. This discrepancy was not found in any other of four similar experiments.

Bursal response (Fig. 3). Two days after anterior body irradiation, the bursa was reduced in size compared to the control size at all dose levels and was signifi-

PARTIAL BODY EXPOSURE



WHOLE BODY EXPOSURE

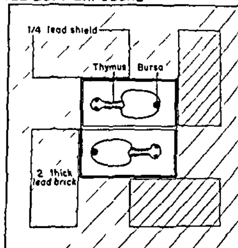


Fig 1 Roentgen rays were delivered to either the whole body (right figure) or the anterior or *posterior half of the body (left figure)* At the midpoint of each of the four quadrants of the 8 inch (20 3 cm) square exposure area the dose varied by less than 1 % Either the bursa or the thymus of each chick was centered at the midpoint of the quadrants

Klager Hatchery, Saline, Michigan, shortly after hatching were housed 40 per shelf in a standard chick brooder Purina starter mash and water were available *ad libitum* *Radiation exposures were conducted when the animals were two* weeks of age The chicks were restrained for exposure by means of pliable vinyl tubes 2 inches (5 cm) in length slid over the body The restraining tubes allowed free breathing but maintained the legs in a slightly extended position and prevented wing movement The animals were then secured to paper board slabs measuring 8 inches by 4 inches by 3/4 inches by means of cloth backed foam rubber strips pinned over the legs and neck Although no stress was detected by this procedure alone as measured by reduction in lymphatic organ weight, all animals, including controls, were restrained in this manner for a period of time *equal the longest exposure time*

Dissection On the second, fifth, and eighth days after exposure, eight animals per group were killed, weighed and the thymus and bursa removed, and weighed to the nearest 0 1 mg Because a direct relationship exists in the young chicken between lymphatic organ *weight and body weight, absolute organ weights were* converted to mg /100 g body weight Since even the young chicken is capable of retaining several grams of food in its crop, animals to be dissected were removed from the brooder before feeding began in the morning Any food found in the crop was removed before body *weight measurements were taken*

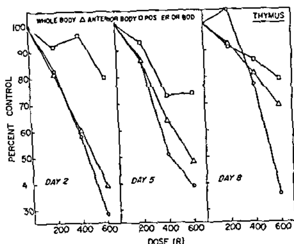


Fig 2 Thymic weights following whole body anterior body or posterior body irradiation

Results

Thymic response (Fig 2) Posterior body exposure resulted in a decrease in thymic weight compared to control weights at all dose levels measured 2 days post exposure At 400 R and 600 R the decrease in thymic weight was maximum on the fifth day post exposure while weight loss was similar on each day after 200 R

The two day thymic weight dose responses were approximately linear for both whole body and anterior body irradiation with ED $_0$ (50 % depression) values of 450 to 500 R The 200 R and 400 R weights were not different in the groups but at 600 R the average weight of the whole body group was significantly less than that of the anterior body group ($p < 0\,5$) Five days post exposure the weights were similarly different at 600 R ($p < 0\,05$) and at 400 R as well ($p < 0\,05$) The five day ED $_0$ values were 425 (whole body exposure) and 575 R (anterior body exposure)

Eight days post exposure two differences were apparent between the whole body and anterior body groups The average thymic weight of the whole body and anterior body group was larger at 200 R ($p < 0\,05$) and the average thymic weight of the anterior body group was considerably larger at 600 R ($p < 0\,01$) than that of the whole body group The difference noted at 200 R was contra dictory to the generally observed equal or greater depression of lymphatic tissue due to whole body irradiation compared to partial body irradiation This discrepancy was not found in any other of four similar experiments

Bursal response (Fig 3) Two days after anterior body irradiation the bursa was reduced in size compared to the control size at all dose levels and was signifi

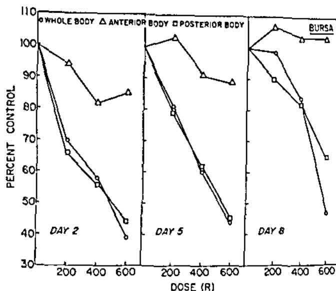


Fig 3 Bursal weights following whole body, anterior body or posterior body irradiation

cantly less at 400 R and at 600 R ($p < 0.05$) Five days post exposure the 400 R and 600 R bursal weights were still below control weights and eight days post exposure the bursal weights at all dose levels were slightly above those in the control group

No difference was seen between whole body exposure and posterior body exposure except at 600 R on the eighth day when the bursa of the whole body group was significantly smaller ($p < 0.05$) For the whole body and posterior body exposures the two day ED_{50} was 475 R to 500 R and the five day ED_{50} was 500 R to 550 R

Discussion

Direct (scopal) damage The best estimate of the direct or scopal radiation damage and subsequent recovery to the chick lymphatic tissue was obtained from the thymic response to anterior body irradiation In these animals the thymus along with few other radiosensitive tissues and approximately one third of the total chick volume was exposed, resulting in only a small amount of abscopal damage The thymus weight dose response was approximately linear at maximum depression on the second day after irradiation The ED_{50} value at this time was approximately 500 R On the fifth day and eighth day recovery was evident at each dose and the thymus weight dose relationship remained essentially linear

Abscopal damage Two analyses of the included data were used to determine the presence and extent of abscopal damage

1 Any difference between the thymic weights of the group whose posterior

half was irradiated and the thymic weights of the control animals was assumed to be the result of abscopal damage Similarly any decrease in bursal weights below control values as the result of anterior body irradiation was considered to represent abscopal damage

Two days after anterior body exposure the bursa was reduced in weight and progressive recovery was evident on the fifth and eighth days. These results were interpreted as indicating an abscopal effect acting shortly after radiation exposure Since no similar injury has been reported for mammals this will here be termed chick type damage As would be expected when little of the gastro-intestinal tract was exposed no additional decrease in the size of the bursa was seen five days after exposure when typical mammalian type abscopal damage is normally evident

The thymus was reduced below control levels on the second day following posterior body irradiation and showed about the same extent of chick type damage as the bursa in the anterior body exposures Whereas the bursa showed progressive recovery on the fifth and eighth days the thymus showed an additional weight loss on the fifth day and only slight recovery on the eighth day This later depression and lack of recovery in the group whose gastro-intestinal tract was included in the lack of recovery in the group to be indicative of mammalian type abscopal damage

2 Any additional decrease in organ size due to whole body irradiation as compared to partial body irradiation was also considered to be the result of abscopal damage This interpretation was valid only when the organ considered was under the beam during the partial body exposure as with the thymus during anterior body exposure and the bursa during posterior body exposure If the scopal and abscopal damages were strictly additive the whole body values would be expected to be reduced below the partial body values by an amount proportional to the degree of depression below the control level seen in the case of the bursa following anterior body exposure or in the case of the thymus following posterior body exposure as was described above

Only on the eighth day and at 600 R was the bursal weight less following whole body irradiation than following posterior body irradiation. From the 2 day and 5 day lines (*Fig* 3) this can be seen to be primarily the result of recovery in the group whose posterior half was exposed

Two days following exposure to 600 R the thymus was smaller in the whole body irradiation group than in the anterior body irradiation group indicating the presence of chick type abscopal damage On the fifth day the same relationship was again seen at 600 R and also at 400 R suggesting at least the mammalian type abscopal damage On the eighth day the thymus only of the 600 R group was smaller following whole body irradiation than following anterior body irra

diation The difference, however, was greater than at any other time, suggesting that the 'mammalian type' abscopal damage continued and possibly increased at *this high dose to the whole body*, while recovery was occurring from the scopal damage as seen by the increase in size of the thymuses of the animals whose anterior halves were exposed

The abscopal depression of chick lymphatic tissue was not nearly as apparent by this second analysis as it was by the first In the thymus, however, both types of abscopal damage could be seen to occur although only at the higher doses Although the whole body exposures were more effective than the partial body exposures in some instances in reducing the weight of the lymphatic organ under the beam, the scopal and abscopal effects appeared to be additive at the most This suggests that the abscopal and scopal types of damage act independently

It would appear, then, that in the chicken, both scopal and abscopal damage contribute significantly to the overall degree of post irradiation involution of lymphatic organs with the abscopal damage responsible for as much as 20 to 30 % of the involution seen following whole body exposure In both cases the degree of damage is dose related It is suggested that in addition to the abscopal *damage seen in mammals and related to gut damage that a second and earlier* appearing abscopal effect is present in the chicken This abscopal damage occurs *even when the gastro intestinal tract is shielded from the radiation beam* For this damage to effect a decrease in lymphatic organ weight as early as two days after exposure would require action on the lymphatic tissues within a short time of exposure JACQUEZ & KARNOFSKY (1950) and STEARNER (1951) have described vascular lesions in the chicken which lead to death within 24 hours of exposure to less than 1 000 R It is quite possible that the same type of lesions, occurring at sublethal doses, produce an abscopal effect on the chick lymphatic organs

SUMMARY

Ten day old white leghorn cockerels were exposed to 200 R 400 R or 600 R of roentgen rays delivered to the cephalic half the caudal half or to the whole body Thymic and bursal weights were obtained 2 5 and 8 days after exposure Partial body exposures indicate that 20 to 30 % of the post irradiation weight loss in the lymphatic organs may be the result of abscopal processes and that in the chicken, this damage is evident as early as two days after exposure

ZUSAMMENFASSUNG

Zehn Tage alte weisse Leghorn Hahnchen wurden mit 200 R, 400 R oder 600 R von Rontgenstrahlen entweder auf die Kopfhalfte die Schwanzhalfte oder den ganzen Korper gerichtet bestrahlt Das Gewicht von Thymus und Bursa wurden 2 5 und 8 Tage nach der Bestrahlung festgestellt Teilkorperbestrahlung des Korpers zeigt dass 20 bis 30 % des

Gewichtsverlustes der lymphatischen Organe nach der Bestrahlung Ergebnisse von Fern Wirkungen sein kann und dass beim Hahnchen diese Schadigung bereits zwei Tage nach der Bestrahlung deutlich wird

RÉSUMÉ

L auteur a expose des jeunes coqs Leghorn blancs ages de 10 jours a une irradiation de 200 R 400 R ou 600 R de rayons de roentgen sur la moitie cephalique la moitié caudale ou la totalite du corps. Il a pese le thymus et la bourse de Fabricius 2 5 et 8 jours apres l irradiation. L irradiation partielle du corps montre que 20 à 30 % de la perte de poids des organes lymphatiques apres l irradiation peut etre le résultat de processus qui se passent en dehors du territoire irradie et que chez le poussin cette lesion est evidente des le deuxième jour apres l irradiation

REFERENCES

BOND V P SWIFT M N TAKETA S T et coll Effect of localized deuteron irradiation of the rat Amer J Physiol 174 (1953) 259

CORP M J LAW A W and MOLE R H Abdominal irradiation and the thymys of the adult rat the relative importance of the adrenal glands and of scattered radiation Amer J Roentgenol 85 (1961) 550

GOOD R A GABRIELSEN A E PETERSEN R. D A et coll The development of the central and peripheral lymphoid tissue ontogenic and phylogenetic consideration The thymus Experimental and clinical studies CIBA Foundation Symposium Little Brown and Co Boston 1966

JACQUEZ J A and KARNOFSKY D A The toxicity and pathological effects of roentgen rays in the chicken Amer J Roentgenol 64 (1950) 289

LAW A W and MOLE R H Direct and abscopal effects of x radiation on the thymus of the weanling rat Int J Radiat Biol 3 (1961) 233

LEBLOND C P and SEGAL G Differentiation between direct and indirect effects of roentgen rays upon organs of normal and adrenalectomized rats Amer J Roentgenol 47 (1942) 30?

MONTOUR J L Radiation induced involution of the lymphatic organs of the young chicken Acta radiol Ther Phys Biol 7 (1968) 337

STEARNER S P Effects of variation in dosage rate of roentgen rays on survival in young birds Amer J Roentgenol. 65 (1951) 265

Book reviews

CANCER OF THE HEAD AND NECK By W S MacComb and G H Fletcher 598 pages with 342 figures and 153 tables Williams & Wilkins Baltimore 1967 Price $ 28 50

It is stated in this book that twenty thousand patients with cancer of the head and neck were examined over a 10 year period at the M D Anderson Hospital and Tumor Institute in Houston This large material has been carefully investigated Both the head and neck surgeon William MacComb and the radiotherapist Gilbert Fletcher are well known and appreciated by all who deal with tumors of the head and neck They have previously published a book (1962) entitled Radiation therapy in the management of cancers of the oral cavity and oropharynx in which emphasis was placed mainly on radiation treatment this second book forms a complement The clear and simple style and the excellent disposition of the text make both books easy to read the many good illustrations and valuable case reports add to its worth

The twenty two chapters by no less than thirty six authors cover all that is of practical importance about cancer of the head and neck

The work is concluded with a chapter entitled *Method of computing end results* This ought to have come first in the book It should be remembered that statistical data from the M D Anderson Hospital are usually not directly comparable with our own which are computed by the determinate method The M D Anderson Hospital uses the Berkson Gage method and with this the figures for cures are somewhat higher than with the determinate method

A Swedish radiotherapist notices the lack of puncture cytology in a book of this kind We have today become accustomed to obtaining quick diagnoses from lymph nodes by means of fine needle biopsy It seems not entirely unimportant whether the diagnosis is obtained by excision of a lymph node metastasis or by puncture with a 0 6 mm needle seeing that Fletcher points out that an extra radiation dose should be given over the scar tissue after the operation

Over one year about 17 per cent of the cases with intra oral cancer were sent in by dentists who had detected the tumor first (In order to make it easier for the dentists to recognize these tumors a brochure containing a large number of color prints showing malignant tumors in the oral cavity has been issued by the Swedish Cancer Society and distributed in Sweden Norway and Finland)

It is interesting to consider the specialists the authors think should be included in a team for treating tumors of the head and neck general surgeon otolaryngologist plastic surgeon oral surgeon dentist maxillofacial prosthodentist radiotherapist radiologist psychiatrist speech therapist and physiatrist!

There is thus every reason to agree with what Lee Clark director of the M D Anderson Hospital says in the preface The management of the patient with head and neck cancer as practiced today in its finest form is of necessity confined to a few centers which specialize in the care of cancer patients This circumstance results from the complex nature of head and neck cancer its disabling effects the need for a teamwork approach and the tremendous amount of clinical experience required to perfect and preserve the technical skill and continued advancement needed to improve the therapeutic art

Folke Jacobsson

BASIC MEDICAL RADIATION PHYSICS By L Stanton 644 pages with 200 figures and 110 tables Butterworths London 1969 and Meredith Corporation New York 1969 Price 110 shillings

The preface of this book indicates that it is directed at physicians working in radiology and nuclear medicine medical students and biologists as well as at those wanting a general idea of the medical uses of ionizing radiation It does not claim to give a complete pre sentation of physical principles and mathematics are kept at a minimum It is also meant as a useful stepping stone to more advanced treatises

As usual in similar works th initial chapters deal with matt r energy and radiation as well as with elementary electricity applied to roentgen apparatus A survey of the proper ties uses and production of roentgen rays is followed by chapters on roentgen ray at tenuation basic radiobiology roentgen dosimetry and the clinical application of measure ment and calculation methods The physics of roentgen diagnostics has its own chapter followed by three chapters on the basic principles of radioactivity and of radioactivity measurements including those in vivo The chapter headed Clinical radionuclide dosimetry is conforming to usual practice more concerned with dose calculation than *measurement* Both sealed and unsealed source dosimetry is treated and useful information is given on sealed sources design

Three chapters are devoted to radiation protection basic concepts methods of minimizing exposure and protection barrier calculation The last chapter appropriately headed Mis cellaneous discusses some ortho- and supervoltage roentgen apparatus telegamma therapy and various accelerators (all this might well have been incorporated in the relevant chapters of the main text) and goes on to ultrasound diagnosis and thermography matters not usually considered to fall within radiation physics

The three appendices consist of a list of references on roentgen depth dose data roentgen ray attenuation and the National Bureau of Standards handbooks on dosimetry and pro- tection there is also a page on sources of error in film dosimetry and a glossary of no less than 42 pages

The reviewer is not sure that the author has fulfilled the task he set himself in the preface The best chapters are those on roentgen ray attenuation on minimizing exposure (one that gives several practical hints for many different types of work) and on calculation of protection barriers The style is most readable and often alleviated by dramatic similes (an inner electron is likened to a daredevil climbing laboriously out of a volcano crater and only able to find rest at the K ledge and so on) There is of course the risk that such tricks may make readers believe they have understood the essentials when in fact they have failed to do so

On the negative side there are numerous repetitions and almost the same thing is often said in widely separated chapters The book is thicker than it need have been with the same factual content The desire to ease the reading has sometimes l d to too lax a terminology (e g on kerma p 166) The glossary on p 62, gives four different defin tions of intensity only one of which is correct

Some notable omissions have been spotted In the section on roentgen machines the three phase type is dismissed in a couple of lines In the dosimetric chapters little is said on other detector types than the ion chamber and wedge filters are omitted Electron beam therapy is mentioned in a line or two in various parts of the book The nuclear medicine chapters deal almost exclusively with how to measure and not why to measure (except

briefly in a table) The physicist, and not only the physician ought surely to know a little about the use of determining the thyroid iodine uptake

It is always easier in a review to be destructively critical than to enumerate all the good points The relative brevity of the positive as compared to the negative side of this review does not invalidate the opinion that the book well earns its correct place on the bookshelf

S en Benner

ACTA RADIOLOGICA

OFFICIAL ORGAN OF THE RADIOLOGICAL SOCIETIES OF
DENMARK, FINLAND, NORWAY AND SWEDEN

Vol 10 Fasc 2 | THERAPY PHYSICS BIOLOGY | 1971 April

CARCINOMA OF THE LARYNX

II Treatment by ^{60}Co supervoltage irradiation

by

KARSTEN JØRGENSEN and ARNE SELL

The radiotherapy of carcinoma of the larynx has been changed in the course of the past decade almost everywhere to supervoltage irradiation. Owing to the short follow up periods little is yet known of the results, but the relatively few reports seem promising.

These neoplasms commenced to be treated by us with a ^{60}Co unit of kilocurie strength around 1 August 1963. The results obtained during a 5 year period with this unit have been analysed and the expected crude 5 year survival calculated. The object of the present communication is primarily to submit these results, but they will also be compared with those in a group of patients treated during the preceding period primarily by conventional irradiation. Lastly the authors will discuss the possible causes of recurrences following radiotherapy.

Material. A total of 153 patients with carcinoma of the larynx was admitted from 1 August 1963 to 1 August 1969. However, the present material includes only 152 patients, as one died of an intercurrent disorder before treatment of the larynx had been started. Apart from the exclusion of this patient, the material is unselected.

From the Radium Centre (Director Sigvard Kaae) and the E. N. T. Department (Director H. C. Andersen), Århus Municipal Hospital, University of Århus, Denmark. Submitted for publication 11 June 1970.

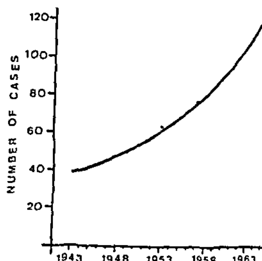


Fig 1 Annual number of cases of carcinoma of the larynx notified to the Danish Cancer Registry The average curve indicates the presumed number of notifications in 1963

Incidence The last publications of the Danish Cancer Registry contained 82 cases of carcinoma of the larynx in 1960 and 107 cases in 1961 (CLEMMESEN & SØRENSEN 1965) No reports have as yet appeared on the annual number of new cases during the period 1963—1968, but it is estimated to be about 120 This estimate is based upon the number of new cases notified annually during the period 1943—1961 (cf Fig 1) The Radium Centre serves a geographic area comprising Jutland (except for the area south of Kongeåen) corresponding to a population of 1 2 millions Table 1 indicates that approximately 30 patients are referred annually, in exact agreement with the number expected from an area housing about a quarter of the Danish population These figures support the assumption that the material is representative of a geographic area having a population of 1 2 million The annual incidence of the disease per 100 000 of the population is then 2 5 (or 1 40 000)

Sex ratio Nine per cent of the patients were women (16/153) and 91 per cent were men (136/152)

Age distribution The age distribution is given in Fig 2 The youngest patient was a woman of 26 and the oldest a man of 90, average age at time of histologic diagnosis being 60 years and 1 month

Histology Histologic examination revealed squamous cell carcinoma in 151 patients and malignant columnar cell adenoma in one patient Eight patients were classified as having carcinoma in situ, all with definite epithelial carcinomatous changes but no evidence of invasive growth

Table I

The 152 patients of the present material grouped according to year of treatment (from August to August) and follow up period so as to calculate the mortality coefficients for the individual years

Year of treatment	Number of patients	Number of survivals after				
		1 year	2 years	3 years	4 years	5 years
1963/64	24	23	20	20	20	18
1964/65	34	29	26	25	23	
1965/66	29	27	22	21		
1966/67	41	36	34			
1967/68	24	19				
Total	152	134	102	66	43	18
Number of deaths		18	13	2	2	2

Symptoms and signs The primary sign was hoarseness in 80 % of the patients (121/152) and irritation in the throat with pain radiating to the homolateral ear in 13 % of the patients (20/152) In the remaining 11 patients the primary signs were cough dysphagia enlargement of cervical lymph nodes or dyspnoea The interval from the onset of the primary symptom or sign until the histologic diagnosis was less than 4 months in 41 4 to 8 months in 32 and more than 8 months in 27 of the patients

Classification The TNM system in the form suggested by UICC (1968) was used Table 2 gives the classification of the 152 patients divided into three main groups supraglottic 41 patients (27 %) glottic 102 patients (67 %) and sub glottic 9 patients (6 %) As is apparent from Table 2 a total of 17 patients (11 % or 17/152) had presumed lymph node metastases on admission Within the three main groups the incidence of cervical node metastases was as follows supraglottic 28 % (11/41) glottic 3 % (3/102), and subglottic 33 % (3/9)

Method of treatment The primary therapeutic principle was almost invariably radiotherapy 147 patients having been treated primarily by radiotherapy and 5 by surgery All the 147 patients were treated by a ^{60}Co unit of kilocurie strength FSD was 80 cm In the early treatment period the field sizes were often 4 cm × 4 cm and 4 cm × 5 cm but during the last three years never less than 6 cm × 6 cm The field size was extended when necessitated by the size of the tumour or by nodal metastases

A treatment shell was made for each patient and in this he was fixed both during the simulation and the treatments. The treatment shell was composed of

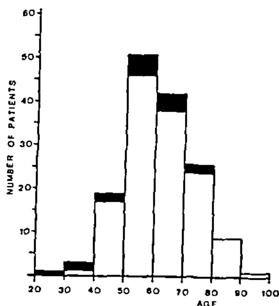


Fig 2 Age distribution at time of histologic diagnosis Black column represents women and white column men

two parts, a posterior part made of plaster and an anterior part of plastic, these were fastened together during the treatment, the plastic part being fastened to the former part A hole was cut in the plastic corresponding to the treatment fields, the marking of the field being done with the aid of a so-called simulator — a fluoroscopic apparatus whose roentgen tube is placed in exactly the same position as the head of the ^{60}Co unit A correct placement of the fields was secured by control photographs of the marked area The dose distribution was calculated for each patient

A compensation filter was used to secure a homogeneous dose in the irradiated area in 26 patients, in nearly all of whom the fields were large Treatment was administered on 5 days of the week to one or two opposing fields a central tumour dose of 6 000 rad over 6 weeks was the aim Extensive subglottic carcinoma in 3 patients and large glottic tumours with respiratory distress in 2 patients indicated primary surgery

Follow up Each patient's reactions were closely observed daily by indirect laryngoscopy during radiotherapy Any suggestion of residue resulted in the patient being admitted about 8 weeks after the completion of the radiotherapy for direct laryngoscopy and possibly biopsy a positive biopsy specimen indicated supplementary surgery Patients with no signs of residual tumour or recurrence were controlled on an out patient basis in a collaboration between the radiotherapists and otologists The follow up will be continued for at least 10 years

Table 2

TNM classification of 152 patients with carcinoma of the larynx treated at Århus from 1 August 1963 to 1 August 1968

		Group				Total
		N0	N1	N2	N3	
Supraglottic	T1	6				
	T2	7				
	T3	9	3			
	T4	8	2	4	2	41
Glottic	T1	39				
	T2	15				
	T3	42				
	T4	3	3			102
Subglottic	T3	3	1			
	T4	3		1	1	9

Therapeutic results. The authors, to express the result of the treatment, calculated the expected crude 5 year survival rate on the lines recommended by NOHRMAN (1953). The material was first divided as in Table 1. The mortality coefficients for the individual years of the follow up period were then calculated with the formula

$$Q_n = \frac{d_n}{d_n + l_n}$$

where Q_n is the mortality coefficient in the n th year, d_n the number of deaths in the n th year and l_n the number of patients alive at the end of n th year. The 5 Q values are then inserted into the formula

$$100 \times (1 - Q_1)(1 - Q_2) \ldots (1 - Q_n)$$

the resulting value being the calculated crude 5 year survival rate. The results of the calculations are plotted as a survival curve in Fig. 2, the calculated crude 5 year survival rate being 65 %. However, this figure carries some uncertainty, partly as only a limited number of patients have a follow up period exceeding 5 years and partly as two deaths from carcinoma took place in the 5th year (*cf.* Table 1). A more correct expression of the 5 year result in the material would be obtained by extrapolating the curve corresponding to the 5th year of the follow up period. As is apparent from Fig. 2, the expected 5 year result is then 70 %. The standard error was calculated on the 3 year result by the Greenwood formula (UICC 1969).

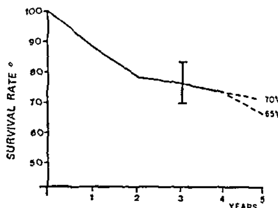


Fig 3 Survival curve for 152 patients with carcinoma of the larynx The standard error calculated and marked twice on the curve

$$P_n \sqrt{\sum \frac{l - p_i}{n_i p_i}}$$

where P_n is the survival rate for the n'th year, p_i the survival rate during the i'th year for patients alive at the beginning of that year, n_i the corresponding number of patients, and Σ the summation of the values for the individual years The standard error was 3 51 %, thus 2 × the standard error is 7 % as plotted in Fig 3

Owing to the short follow up periods the results in the individual groups have not yet been analysed It may, however, be mentioned that the expected 5 year results for the 39 T1N0M0 glottic carcinomas is 97 %, one patient having died 6 months after the treatment without signs of recurrence in the larynx or the neck, but with large mediastinal metastases, presumably due to carcinoma of the lung

Vocal results The authors chose patients, followed for more than 2 years and who had managed with radiotherapy as the only treatment to assess the quality of the voice after ^{60}Co therapy This group comprised a total of 68 patients 61 (90 %) had normal voice function (although several had some deterioration in quality), 6 (9 %) could speak but the quality was distinctly debased and 1 (1 %) was totally aphonic

Side effects of radiotherapy Irritation and dryness of the pharyngeal mucosa occurred in the majority of the patients during the treatment period and the first months after its completion These symptoms were moderate and transient, only 2 patients had marked complaints for more than two years One patient had to have tracheotomy during the treatment because of a laryngeal reaction consisting of oedema and respiratory distress On the other hand, tracheotomy

had been necessary before the treatment in 4 patients because of difficulty in breathing

Acute radiodermatitis did not occur One patient had necrosis of the skin and anterior part of the thyroid cartilage leading to a fistula — presumably because of a complicating abscess in the area A small number of the patients exhibited subcutaneous fibrosis although this was never bothersome

Perichondritis of varying severity was observed in some of the patients with recurrences It rarely occurred was mild and disappeared a few months after the treatment in patients without recurrences Perichondritis never necessitated laryngectomy

Surgical aspects Primary total laryngectomy, as already mentioned was performed in 5 patients because of large subglottic tumours in 3 and glottic neoplasms with respiratory distress in 2 patients

So far (up to 1 August 1969) 60 recurrences after radiotherapy have occurred in the material and of these patients 53 have been treated surgically The operations were distributed as follows 2 patients were subjected to cordectomy, 7 to partial laryngectomy, 2 to partial laryngectomy and later total laryngectomy, 25 to total laryngectomy 23 to total laryngectomy and dissection of cervical nodes and 4 to dissection of cervical nodes

Operative complications were few and no deaths due to operation occurred Severe infection or major necrosis did not occur Eight of the 40 patients subjected to laryngectomy developed fistulae to the hypopharynx or oesophagus six of these were transient, and only two required one or more corrective operations

Frequency of laryngectomy was calculated for patients followed for at least 3 years to obtain a numerical expression of how large a proportion lose laryngeal function This frequency was found to be 24 % (21/87)

An attempt was made to compare the results of primary radiotherapy with a conventional unit and a ^{60}Co unit of kilocurie strength A total of 115 patients were treated for carcinoma of the larynx during the period 1949—1959 of these 96 were primarily irradiated by a conventional unit This group was compared with the 85 patients who were primarily irradiated by a ^{60}Co unit of kilocurie strength during the period 1963—1966 The results are given in Fig 4 which indicate that the therapeutic results for the ^{60}Co group are better than those for the conventional group assessed on the basis of the survival curve The gain is modest and far from significant but at the same time it must be emphasized that the two materials are not comparable in respect to

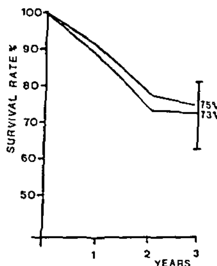


Fig 4 Survival curves for two groups of patients the upper representing a group treated by ^{60}Co supervoltage and the lower curve a group treated by conventional roentgen therapy

classification, as evident from Table 3 The ^{60}Co group includes a relatively larger number of advanced conditions than the conventional group If the number of T4N0M0 cases + the number of cases having nodal metastases (N1 + N2 + N3 cases) is expressed as a percentage of the total number within each of the two groups, the following figures are obtained conventional group 11 % (11/96) and ^{60}Co group 21 % (18/85) The two groups might be rendered comparable by exclusion of analogous groups, e g by excluding the advanced cases *from both groups This was tried, but failed to lead to com*parability The two materials are otherwise comparable as regards symptoms and signs, sex ratio, age distribution, and average age at the time of histologic diagnosis

A good expression of the therapeutic efficacy is how large a proportion of the patients are cured by irradiation alone The 3 year cure rate in the two groups following irradiation alone was 57 % (55/96) in the conventional group and 59 % (50/85) in the ^{60}Co group It must, however, be borne in mind that the ^{60}Co group comprises a considerably larger number of advanced conditions

Recurrences Sixty out of 147 primarily irradiated patients developed recurrences within the control period The case records were perused with a view to finding possible reasons why radiotherapy failed Particular interest was centred on possible technical causes due to underdosage in the area of the tumour or field adjustment, dosage planning, or divergences in the dose time relation After this perusal the site of the recurrences was related to the above factors especially those that might have caused underdosage in part of the tumour area *The possible causes of the recurrence are listed in* Table 4 Of

Table 3

Comparison of TNM classification of 96 patients treated by roentgen irradiation and 85 patients treated by ⁶⁰Co irradiation

		96 patients treated by roentgen irradiation				85 patients treated by Co irradiation			
		N0	N1	N2	N3	N0	N1	N2	N3
Supraglottic	T1	4	1	1		4			
	T2	6	1			5			
	T3	8	1	1		6	2		
	T4	2	3			3	[illegible]	3	2
Glottic	T1	33				19			
	T2	14				13			
	T3	19				18			
	T4	1				1	3		
Subglottic	T3	1				2			
	T4					1	1		

course this table must be accepted only with reserve as there was often the question of an estimate The most important presumed cause is submitted and tabulated for each individual patient several factors may have arisen but this could not be tabulated

It is apparent from the table that in 20 patients (groups 1 to 8) i e 33 %, there may be a suggestion that purely technical causes were to blame On further investigation however it would appear that there can have been only 7 patients i e 11 % (7/60) in whom technical reasons could be said with certainty to have produced local underdosage

The dose time relation was also re evaluated As already mentioned, the planned radiation dose for curative purposes was 6 000 rad administered in 5 fractions weekly during a total period of about 42 days A considerably lower total dose (4 700 3 700 5 300 rad) was administered to 3 patients (group 10) in 2 of whom the treatment had to be interrupted because of severe local symptoms in the third patient the treatment had been planned as palliation right from the start

Ten patients in group 9 were treated over a longer period than the normal approximately 6 weeks without a compensatory increase of the originally planned dose of about 6 000 rad The treatment in 3 patients had been temporarily interrupted because of endolaryngeal reaction and in another 7 patients by Christmas Easter or Whitsun It cannot be claimed with certainty that these factors were the cause of the recurrences

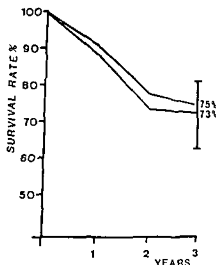


Fig 4 Survival curves for two groups of patients the upper representing a group treated by ^{60}Co supervoltage and the lower curve a group treated by conventional roentgen therapy

classification, as evident from Table 3 The ^{60}Co group includes a relatively larger number of advanced conditions than the conventional group If the number of T1N0M0 cases + the number of cases having nodal metastases (N1 + N2 + N3 cases) is expressed as a percentage of the total number within each of the two groups, the following figures are obtained conventional group 11 % (11/96) and ^{60}Co group 21 % (18/85) The two groups might be rendered comparable by exclusion of analogous groups, e g by excluding the advanced cases from both groups This was tried, but failed to lead to comparability The two materials are otherwise comparable as regards symptoms and signs, sex ratio, age distribution, and average age at the time of histologic diagnosis

A good expression of the therapeutic efficacy is how large a proportion of the patients are cured by irradiation alone The 3 year cure rate in the two groups following irradiation alone was 57 % (55/96) in the conventional group and 59 % (50/85) in the ^{60}Co group It must, however, be borne in mind that the ^{60}Co group comprises a considerably larger number of advanced conditions

Recurrences Sixty out of 147 primarily irradiated patients developed recurrences within the control period The case records were perused with a view to finding possible reasons why radiotherapy failed Particular interest was centred on possible technical causes due to underdosage in the area of the tumour or field adjustment, dosage planning, or divergences in the dose time relation After this perusal the site of the recurrences was related to the above factors especially those that might have caused underdosage in part of the tumour area The possible causes of the recurrences are listed in Table 4 Of

Table 3

Comparison of TNM classification of 96 patients treated by roentgen irradiation and 85 patients treated by ^{60}Co irradiation

		96 patients treated by roentgen irradiation				85 patients treated by Co irradiation			
		N0	N1	N2	N3	N0	N1	N2	N3
Supraglottic	T1	4	1	1		4			
	T2	6	1			5			
	T3	8	1	1		6	2		
	T4	2	3			3	2	3	2
Glottic	T1	33				19			
	T2	14				13			
	T3	19				18			
	T4	1				1	3		
Subglottic	T3	1				2			
	T4					1	1		

course this table must be accepted only with reserve as there was often the question of an estimate The most important presumed cause is submitted and tabulated for each individual patient several factors may have arisen but this could not be tabulated

It is apparent from the table that in 20 patients (groups 1 to 8), i e 33 % there may be a suggestion that purely technical causes were to blame On further investigation however it would appear that there can have been only 7 patients, i e 11 % (7/60) in whom technical reasons could be said with certainty to have produced local underdosage

The dose time relation was also re evaluated As already mentioned the planned radiation dose for curative purposes was 6 000 rad administered in 5 fractions weekly during a total period of about 42 days A considerably lower total dose (4 700 3 700 5 300 rad) was administered to 3 patients (group 10) in 2 of whom the treatment had to be interrupted because of severe local symptoms in the third patient the treatment had been planned as palliation right from the start

Ten patients in group 9 were treated over a longer period than the normal approximately 6 weeks without a compensatory increase of the originally planned dose of about 6 000 rad The treatment in 3 patients had been temporarily interrupted because of endolaryngeal reaction and in another 7 patients by Christmas Easter or Whitsun It cannot be claimed with certainty that these factors were the cause of the recurrences

Table 4

Possible causes of treatment failure in 60 patients all with recurrences after primary radiotherapy of 147 patients

Cause of failure	Group	Number of patients
Technical	1 — Small field size with underdosage posteriorly in the larynx	4
	2 — Small field size with possible underdosage posteriorly in the larynx	1
	3 — Small field size with underdosage anteriorly in the larynx	1
	4 — Small field size with possible underdosage anteriorly in the larynx	3
	5 — Normal field size with underdosage posteriorly in the larynx	9
	6 — Normal field size with possible underdosage posteriorly in the larynx	4
	7 — Use of compensation filter with possible underdosage anteriorly in the larynx	2
	8 — Small field size with correct placement	3
Dose time relation	9 — Strikingly long treatment period	
	A Due to endolaryngeal reaction	3
	B Christmas and other holidays	7
	10 — Small radiation dose	
	A Palliation	1
	B Treatment interrupted due to reaction	2
Tumour biologic	11 — Recurrence in cervical lymph nodes outside treatment field	4
	12 — Recurrence in mediastinum	2
	13 — Recurrence in lungs	1
	14 — *Malignant adenoma hardly radiosensitive*	1
	15 — Widespread carcinoma	11
	16 — No explanation	8

This leaves a major group of recurrences (groups 11 to 16), a total of 27 patients, in whom the recurrence appeared outside the treated area or in whom the growth had been locally much advanced In these latter a reduced oxygen tension in the large neoplasm may have been a cause of reduced radiosensitivity and thereby of the recurrence

No demonstrated or conceivable explanation of the recurrence is evident in the last group of 8 patients (group 16)

Discussion

The analysis of the 5 year material failed to disclose any surprising factors as regards the histology, sex ratio, age distribution, symptomatology, or TNM classification as compared with the findings during the period prior to 1 August

1963 (JØRGENSEN 1970) However there was a relative increase in the number of advanced conditions although without any evidence of a change in the pattern of the disease

The analysis was carried out by the procedure recommended by NOHRMAN (1953) This is closely related to the actuarial method of UICC but requires a 100 % control It fails to utilize the material quite as well as the actuarial method, but is easier in practice as it does not presuppose a status for all the patients on a given day The actuarial method would require for the present material the status for all the patients on 1 August 1969 and this would have involved a great deal of extra work NOHRMAN s procedure also permits cor reaction for mortality from causes other than carcinoma. In the future the patients data will be stored and computer analysed When operating with materials having a 100 % follow up NOHRMAN s method for calculating the survival curve at any time is presumably best applicable in practice

Extrapolation as mentioned had to be done of the last part of the survival curve (Fig 2) because of the small number of patients with a 5 year follow up period and two deaths during the 5th year of follow up which deteriorate the result disproportionately The extrapolation was felt to be permissible as in major series the survival curve after the 3rd year has proved to be practically a straight line, determined by the mortality in the population from causes other than carcinoma of the larynx + a few late deaths from that condition (TASKINEN 1969 JØRGENSEN 1970) The expected 5 year survival result of 70 % will be checked and published in four years time

Few publications of materials from recent years on the supervoltage therapy of carcinoma of the larynx have appeared but the results seem promising (DAHL et coll 1964 CAVANAUGH et coll 1968 HIBBS et coll 1969)

Supplementary secondary surgery after ^{60}Co irradiation posed no special problems The frequency of laryngectomy proved to be low (24 % *in patients* with a minimum survival of 3 years) and is not expected to have reached 30 % when a 5 year follow up period has been obtained for all patients as only a few late laryngectomies are being done

In U S A in particular, there has been a marked trend towards primary surgery However without analyses from that country of the same nature and from the same *period* as the present one, it is difficult to compare the two procedures ALEXANDER (1966) SMITH (1966) SPENCER (1967), VON ESSEN 1968) and HUTCHINSON (1968) have published series from U S A from the 1950 s up to the beginning of the 1960 s The composition as regards classification does not *appear to differ* much from ours the frequency of total laryngectomy in these series ranged from 55 to 75 % The survival figures in the present material compare favourably The procedure of primary radio-

therapy of carcinoma of the larynx therefore appears to be a better method, both as regards survival and preservation of laryngeal function

As already mentioned, an attempt was made to compare the present material with one of patients who had been treated primarily by conventional radiotherapy However, the two materials were not comparable as the ^{60}Co material included a considerably larger number of advanced neoplasms Nevertheless the survival curve for the ^{60}Co group was better although not significantly so (Fig 4) Radiotherapy with a ^{60}Co unit of kilocurie strength and a simulator for marking the fields and individually tailored, fixed treatment shells thus seems to be superior to conventional radiotherapy

Analysis of the 60 recurrences after radiotherapy indicated that technical factors might have contributed to the recurrence in 33 % of the patients However, divergences in the field technique occurred only during the first 3 years of the 5 year period It is pointed out also that an altered fractionation of the dose, prolonging the treatment period because of Christmas and other holidays, may have exerted an influence upon the recurrence A careful field technique and due regard to the dose time relation ought to improve the therapeutic results further

Conclusion

A material of 152 patients with carcinoma of the larynx is presented, 147 of these were primarily treated by irradiation with a ^{60}Co unit of kilocurie strength during the period 1 August 1963 to 1 August 1968 The expected crude 5 year survival result was calculated to be 70 % and the frequency of laryngectomy for recurrence was 24 % These results were compared with those in a group of patients treated by conventional roentgen therapy The survival curve for the ^{60}Co-treated partients was better in spite of the fact that this group included a relatively larger number of advanced conditions

Perusal of the records of 60 patients with recurrence following radiotherapy revealed that technical causes (field size and placement) might possibly have contributed to this failure in a third of the patients Definite technical causes were demonstrable, however in only 7 of the patients, or 11 % (7/60)

The results are compared with recent materials from U S A treated predominantly by surgery Primary radiotherapy appears to afford better survival results and in addition twice as many patients by avoiding laryngectomy preserve laryngeal function

The method of calculation in working out the survival curves is discussed The Nohrman method used in the present investigation proved easy and is presumably better for future computer analysis than the actuarial method recommended by UICC

SUMMARY

The results of the primary treatment of 147 patients with carcinoma of the larynx with a ^{60}Co unit of kilocurie strength during a 5 year period are reported and compared with those in a material treated by conventional roentgen therapy. It is evident that primary radiotherapy appears to provide better survival and improved laryngeal results than laryngectomy.

ZUSAMMENFASSUNG

Die Resultate einer vergleichenden Untersuchung von 147 Patienten mit Kehlkopfkarzinom nach primärer Behandlung mittels einer ^{60}Co Anlage von Kilocuriestärke und mittels gewöhnlicher Röntgenbestrahlung werden berichtet. Es zeigte sich, dass die primäre Strahlenbehandlung eine längere Überlebungszeit und bessere Kehlkopfsfunktion als Laryngektomie aufweist.

RÉSUMÉ

Les auteurs présentent les résultats du traitement primitif du cancer du larynx pendant une période de cinq ans sur 147 malades au moyen d'une unité de cobalt thérapie d'un kilocurie et les comparent avec les résultats de sujets traités par la roentgen thérapie classique. Il est évident que la radio thérapie primitive paraît donner une meilleure survie et des résultats larynges meilleurs que laryngectomie.

REFERENCES

Alexander F. W. and Cassady C. L.: 306 laryngeal carcinomas. Staging and end results. Arch. Otolaryng. 83 (1966), 602.

Cavanaugh O., Ferguson G. B., Jordan R. C. et coll.: Treatment of early carcinoma of the vocal cord. N. C. med. J. 29 (1968), 212.

Clemmesen J.: Statistical studies on the aetiology of malignant neoplasms. Acta path. micro-biol. scand. (1965). Suppl. No 174, part 2, p. 6.

Dahl O., Jacobsson F. and Walstam R.: Telegamma therapy of laryngeal carcinoma. Acta Un. int. Canc. 20 (1964), 1735.

von Essen C. F., Shedd D. P., Connelly R. R. and Eisenberg H.: Cancer of the larynx in Connecticut 1935—1959. Cancer 22 (1968), 1315.

Hibbs G. G., Ying D. and Hendrickson F. R.: Radiotherapy for early stages of vocal cord cancer. Ann. Otol. (St. Louis) 78 (1969), 319.

Hutchinson T. H., Forman J. B. and Fitz Hugh G. S.: A clinical review of carcinoma of the larynx. University of Virginia Hospital 1935—1964. Virginia med. Mth 95 (1968), 328.

Jørgensen K.: Carcinoma of the larynx. I. Treatment mainly by primary *irradiation*. Acta radiol. Ther. Phys. Biol. 9 (1970), 401.

Nohrman B. A.: Survival rate calculation. Acta radiol. 39 (1953), 78.

Smith R. R., Caulk R. M., Russell W. O. and Jackson C. L.: End results in 600 laryngeal cancers using the American Joint Committee's proposed method of stage classification and end results reporting. Surg. Gynec. Obstet. 113 (1961), 435.

Spencer J. T.: Cancer of the larynx. Laryngoscope 77 (1967), 969.

Taskinen P. J.: Radiotherapy and TNM classification of cancer of the larynx. Acta radiol. (1969). Suppl. No. 287.

UICC. Union Internationale Contre le Cancer: TNM classification of malignant tumours. Geneva 1968.

FROM THE DEPARTMENTS OF RADIOTHERAPY (DIRECTOR PROF M LINDGREN) AND RADIATION PHYSICS (DIRECTOR PROF K LIDEN), THE UNIVERSITY HOSPITAL, LUND, SWEDEN

MANTLE TREATMENT OF HODGKIN'S DISEASE

Preliminary report of side effects and early results

by

TORSTEN LANDBERG, GUDRUN SVAHN-TAPPER and KNUT WINTZELL

The rationality of irradiation not only of involved but also of adjacent, clinically apparently uninvolved lymph node groups in patients with local Hodgkin's disease, has been stressed by PETERS (1950, 1966), PETERS & MIDDLEMISS (1958), KAPLAN (1962, 1966), SALZMAN et coll (1964), JELLIFFE (1965) and NOBLER (1968), and others

In recent years, the mantle technique has been widely used in the treatment of supradiaphragmatic disease The recommended absorbed dose in the target for this technique is generally about 4 000 rad in 4 weeks (For further comments on the modification of technique and dose level, reference is made to SVAHN TAPPER & LANDBERG 1971)

SALZMAN et coll wrote the symptoms, mainly secondary to irradiation of the upper respiratory tract segment, are tolerable and rarely require any interruption in the treatment schedule FULLER (1967) stated that complications of intensive irradiation for Hodgkin s disease were rare NOBLER wrote in general, the local side effects are relatively mild and transient in nature and can be controlled with appropriate symptomatic medication

Certain side effects have attracted special interest, namely oesophagitis, irradiation pneumonitis, irradiation pericarditis, irradiation myelitis and hematologic complications

KAPLAN (1962) and KAPLAN & ROSENBERG (1966) found that transient

---

Submitted for publication 26 January 1970

oesophagitis was common during treatment of the mediastinal region and that it sometimes persisted for a few weeks

KAPLAN (1962) described a patient in whom massive mediastinal and cardiac involvement was present The absorbed dose in the tumour was carried to 4 000 rad and the field had to include much of the pulmonary parenchyma on both sides The patient died from pulmonary radiation fibro is six years after treatment and no evidence of residual or recurrent Hodgkin s disease was found at autopsy KAPLAN later (1966) remarked approximately one third of patients experience a dry, irritating cough during the first few months following com pletion of mediastinal treatment often associated with radiographic exaggeration of the pulmonary vascular markings indicative of paramediastinal radiation pneumonitis By careful collimation and periodic field reshaping the severity of such reactions has been minimized and they usually have cleared promptly leaving little or no functional incapacity and a normal chest radiograph

KAPLAN & ROSENBERG (1966) in three out of thirty seven patients noted a transient acute pericarditis within the first 6 to 12 months after treatment, and in seven out of the thirty seven patients reported mild transient numbness and/or tingling in the fingers and toes accentuated by flexing the neck (Lhermitte s sign) presumably attributable to a transient cervical or dorsal myelopathy None of the latter patients had paralysis

KAPLAN (1966) found that cutaneous reactions during treatment are gener ally negligible and the later condition of the skin is excellent

SALZMAN et coll (1964) found that radiation of the upper lymphoma field effected a fall in the white blood cell count to below 5 000 in 21 per cent of the patients KAPLAN (1966) stated leukopenia and thrombocytopenia occur during wide field treatment but revert to normal within a few weeks or months in most instances KAPLAN & ROSENBERG (1966) reported that there have been no deaths due to hematopoietic injury They noticed no unusual susceptibility to bacterial infections but several patients developed herpes zoster, which was sometimes unusually severe

NOBLER stated the only major problem which remains unresolved is bone marrow depression This tends to be minimal during a first course of ir radiation for example to the upper trunk lymph nodes but somewhat more of a problem when this is followed by a second course of treatment to the major lymph node bearing areas of the lower trunk A mild leukopenia with the white blood count decreasing to 3 000 to 4 000 cells per mm^3 often develops during the first course of irradiation This rapidly returns to normal usually within 2 to 4 weeks. A thrombocytopenia parallels the leukopenia with the lowest counts usually reaching no lower than 100 000 per mm^3 followed by a imilar rise to normal levels Anemia is rarely significant In spite of the leukopenia and

FROM THE DEPARTMENTS OF RADIOTHERAPY (DIRECTOR PROF M LINDGREN) AND RADIATION PHYSICS (DIRECTOR PROF K LIDEN), THE UNIVERSITY HOSPITAL, LUND, SWEDEN

MANTLE TREATMENT OF HODGKIN'S DISEASE

Preliminary report of side effects and early results

by

TORSTEN LANDBERG, GUDRUN SVAHN-TAPPER and KNUT WINTZELL

The rationality of irradiation not only of involved but also of adjacent, clinically apparently uninvolved lymph node groups in patients with local Hodgkin's disease, has been stressed by PETERS (1950, 1966), PETERS & MIDDLEMISS (1958), KAPLAN (1962, 1966), SALZMAN et coll (1964), JELLIFFE (1965) and NOBLER (1968), and others

In recent years, the mantle technique has been widely used in the treatment of supradiaphragmatic disease The recommended absorbed dose in the target for this technique is generally about 4 000 rad in 4 weeks (For further comments on the modification of technique and dose level, reference is made to SVAHN TAPPER & LANDBERG 1971)

SALZMAN et coll wrote the symptoms, mainly secondary to irradiation of *the upper respiratory tract segment, are tolerable* and rarely require any interruption in the treatment schedule FULLER (1967) stated that complications of intensive irradiation for Hodgkin s disease were rare NOBLER wrote in general, the local side effects are relatively mild and transient in nature and can be controlled with appropriate symptomatic medication

Certain side effects have attracted special interest, namely oesophagiti , irradiation pneumonitis, irradiation pericarditis, irradiation myelitis and hematologic complications

KAPLAN (1962) and KAPLAN & ROSENBERG (1966) found that transient

Submitted for publication 26 January 1970

radiation of the liver and spleen Different regions were treated either in sequence or alternating over a period of 3 to 5 months

This preliminary communication is concerned with the side effects and early results of mantle treatment of patients with Hodgkin s disease

Material and Methods

Material The series consisted of 12 patients (5 males and 7 females) aged 17 to 65 (median 25) with Hodgkin s disease in whom mantle treatment was started before March 1st 1968 (Fig 1)

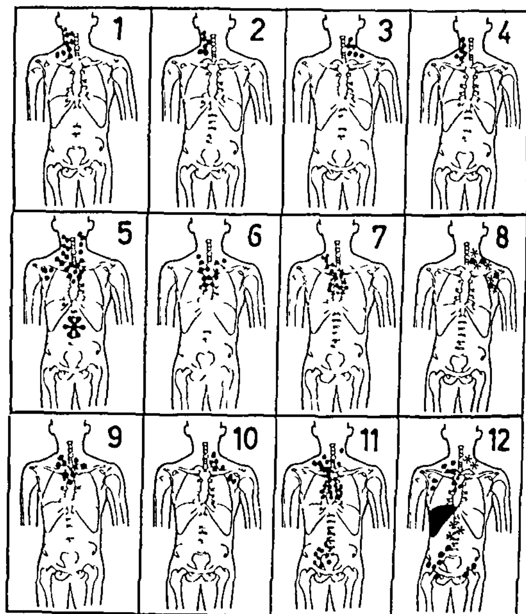
The histologic types of disease (LUKES et coll 1966) were lymphocytic pre dominance in three (Nos 4 8 and 10) nodular sclerosis in two (Nos 5 and 7) and mixed cellularity in the remaining seven patients Before the first mantle treatment roentgen examination of the chest had been performed in all the patients and of the skeleton in eight lymphography in eleven inferior cavography in eight scintigraphy of the liver with colloidal ^{198}Au in all and of the spleen with ^{197}Hg BMHP in five patients Epipharyngoscopy had been carried out in nine patients and microscopy of the sternal marrow aspirate in eleven patients Fig 1 shows the manifestations present at the first mantle treatment as well as those treated earlier (Nos 8 and 12) and diagnosed later (No 5) Clinically the disease was local in ten (Nos 1 to 10) whereas intra abdominal spread had been diagnosed in two (Nos 11 and 12) patients Mediastinal in volvement had been detected in six of the patients and in three of these (Nos 6 7 and 11) the pulmonary hila were enlarged at the roentgen examination

Dosage The treatments were given according to the principles described by SVAHN TAPPER (1970) and by SVAHN TAPPER & LANDBERG (1971) In four of the patients (Nos 8 9 10 and 11) beam flattening filters were used whereas in the remaining eight patients the variation of the absorbed dose in the target was reduced solely by successive reductions of the fields

Follow up After the conclusion of treatment the patients were seen once a month during the first half year and then every second month The examination included roentgen examination of the chest and detailed blood tests

Results and Discussion

Dosage The irradiations were given with ^{60}Co at an SSD of 130 cm The absorbed dose in the target was intended to correspond to 4 000 rad over 4 to 5 weeks In a 5 days-a week scheme this means 200 to 160 rad in each of the fractions but to avoid severe nausea and fatigue more fractions were used in the present series



* = earlier ● = present ✱ = later manifestations

Fig. 1. Twelve patients with Hodgkin's disease. Clinical manifestations treated earlier, present at the beginning of mantle treatment, or diagnosed later.

thrombocytopenia, infections or bleeding episodes are exceedingly rare complications."

JELLIFFE mentioned the possibility of inducing leukaemia in cured patients.

In patients with generalised disease, KAPLAN & ROSENBERG gave treatment both with the mantle technique and an inverted Y shaped field, as well as ir

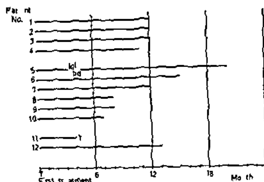


Fig 3 Further clinical course in all the twelve patients after the beginning of mantle treatment the plus sign denotes death

Reactions of skin and mucous membranes Four of the eleven patients who received full mantle treatment had symptoms of mucositis of the floor of the mouth and two complained of symptoms of oesophagitis at the conclusion of treatment These symptoms disappeared within a few weeks None of the eleven patients had severe symptoms of laryngitis In three patients a cervical skin reaction extending into the axillary folds was noticed at the end of the treatment, and in all three the skin reaction was only dryness in the remaining eight patients only a slight tanning was observed All patients had radiation alopecia of the back of the head up to the level of the external occipital protuberance and in the five males also of the lower part of the face for 5 to 7 months after the end of treatment

Follow up The further clinical course of the twelve patients is recorded in Fig 3 In patient No 11, the disease was advanced at the time of the first mantle treatment (see Fig 1) It was decided to irradiate the abdominal lymphomas simultaneously The response to treatment was poor and the patient died (in high grade fever) 4 months after the first mantle treatment Autopsy was not performed In patient No 5 repeat lymphography 4 months after the mantle treatment revealed abdominal lymphomas Two months later this patient was given radiotherapy with an inverted Y-shaped field technique up to an absorbed dose in the target of 4 000 rad The remaining ten patients felt well and presented no further signs of disease about (mean) 12 months after the first mantle treatment No local recurrences have been observed.

Two patients received therapy with cytostatics In one (No 12) such treatment was started 3 months after the first mantle treatment and in the other (No 5) it was commenced 18 months after the first mantle treatment because of peripheral facial palsy which originally but not later, was thought to be due to Hodgkin s disease

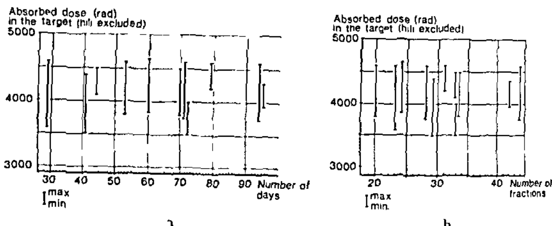


Fig 2 Total absorbed dose (rad) in target (hilar region excluded) in the eleven patients given *full mantle treatment* related to the number of days (a) and to the number of fractions given (b)

In eight of the twelve patients one field was irradiated with each fraction, the peak absorbed dose in the central beam being (mean) 225 rad In four patients, both fields were irradiated with each fraction, the peak absorbed dose in the central beam then being (mean) 140 rad Three patients were treated in one series over (mean) 38 days and with (mean) 28 fractions The treatment in nine patients was given as a split course with about two thirds of the fractions in the first series and an interval of (mean) 34 days between the two series For the split course treatment, irradiation was given during (mean) 75 days with (mean) 31 fractions

In one patient (No 11), who also had abdominal lymphomas, a lower total dose was administered, whereas in the remaining eleven patients the full mantle treatment was given Two of these eleven patients experienced however severe nausea during treatment and three complained of considerable weakness

Fig 2 sets out the total absorbed dose (rad) in the target for the eleven patients receiving full mantle treatment The absorbed doses are related to the number of days (Fig 2a) and to the number of fractions given (Fig 2b) The absorbed doses were calculated on the assumption of homogeneous unit density tissue, and no regard was taken to the presence of lung tissue in the hilar regions The maximum value never exceeded 4 650 rad and the minimum never fell below 3 500 rad in any of the patients In the three patients in whom treatment was given in one series, the total number of days was 29, 41 and 44 respectively The wide range in the number of days and the number of fractions, despite the fairly even level of the absorbed dose in the different patients, mirrors the individual tolerance The absorbed dose in the spinal cord was 4 500 to 3 800 rad in a period of at least 4 weeks *The total absorbed dose in the eyes was less than 100 rad*

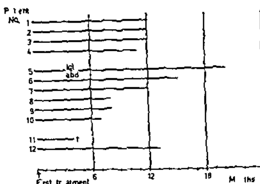


Fig 3 Further clinical course in all the twelve patients after the beginning of mantle treatment the plus sign denotes death

Reactions of skin and mucous membranes Four of the eleven patients who received full mantle treatment had symptoms of mucositis of the floor of the mouth and two complained of symptoms of oesophagitis at the conclusion of treatment These symptoms disappeared within a few weeks None of the eleven patients had severe symptoms of laryngitis In three patients a cervical skin reaction extending into the axillary folds was noticed at the end of the treatment and in all three the skin reaction was only dryness in the remaining eight patients only a slight tanning was observed All patients had radiation alopecia of the back of the head up to the level of the external occipital protuberance and in the five males also of the lower part of the face for 5 to 7 months after the end of treatment

Follow-up The further clinical course of the twelve patients is recorded in Fig 3 In patient No 11 the disease was advanced at the time of the first mantle treatment (see Fig 1) It was decided to irradiate the abdominal lymphomas simultaneously The response to treatment was poor and the patient died (in high grade fever) 4 months after the first mantle treatment Autopsy was not performed In patient No 5 repeat lymphography 4 months after the mantle treatment revealed abdominal lymphomas Two months later this patient was given radiotherapy with an inverted Y shaped field technique up to an absorbed dose in the target of 4 000 rad The remaining ten patients felt well and presented no further signs of disease about (mean) 12 months after the first mantle treatment No local recurrences have been observed

Two patients received therapy with cytostatics In one (No 12) such treatment was started 3 months after the first mantle treatment and in the other (No 5) it was commenced 18 months after the first mantle treatment because of peripheral facial palsy which originally, but not later was thought to be due to Hodgkin s disease

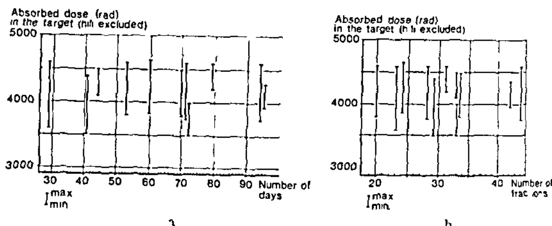


Fig 2 Total absorbed dose (rad) in target (hilar region excluded) in the eleven patients given full mantle treatment related to the number of days (a) and to the number of fractions given (b)

In eight of the twelve patients one field was irradiated with each fraction, the peak absorbed dose in the central beam being (mean) 225 rad In four patients, both fields were irradiated with each fraction, the peak absorbed dose in the central beam then being (mean) 140 rad Three patients were treated in one series over (mean) 38 days and with (mean) 28 fractions The treatment in nine patients was given as a split course with about two thirds of the fractions in the first series and an interval of (mean) 34 days between the two series For the split course treatment, irradiation was given during (mean) 75 days with (mean) 31 fractions

In one patient (No 11), who also had abdominal lymphomas, a lower total dose was administered, whereas in the remaining eleven patients the full mantle treatment was given Two of these eleven patients experienced however severe nausea during treatment and three complained of considerable weakness

Fig 2 sets out the total absorbed dose (rad) in the target for the eleven patients receiving full mantle treatment The absorbed doses are related to the number of days (Fig 2a) and to the number of fractions given (Fig 2b) The absorbed doses were calculated on the assumption of homogeneous unit density tissue, and no regard was taken to the presence of lung tissue in the hilar regions The maximum value never exceeded 4 650 rad and the minimum never fell below 3 500 rad in any of the patients In the three patients in whom treatment was given in one series, the total number of days was 29, 41 and 44, respectively The wide range in the number of days and the number of fractions, despite the fairly even level of the absorbed dose in the different patients, mirrors the individual tolerance The absorbed dose in the spinal cord was 4 500 to 3 800 rad in a period of at least 4 weeks The total absorbed dose in the eyes was less than 100 rad

Cardiac reactions No signs of pericarditis or any other cardiac conditions could be detected except in one patient (No 1), who had continuous tachycardia Electrocardiagrams were recorded in eight of the patients 8 to 15 months after the first mantle treatment and in three of these it had also been recorded before treatment Two (Nos 5 and 8) of the eight patients had slight ST T changes which however were considered to be of no pathologic significance Patient No 1 had tachycardia and an R S ratio exceeding 1 0 in lead V_1 which might signify right ventricular hypertrophy The ECG was completely normal in the other five patients

Pulmonary reactions Roentgenologic signs of radiation pneumonitis were present in nine of the eleven patients in whom the follow up was at least 6 months Pneumonitis was in general first diagnosed 3 to 5 months after the first mantle treatment at roentgen examination of the chest but in one patient (No 12) as early as after a month Four of the nine patients in whom roentgen examination had revealed pneumonitis had no symptoms, but five had cough and fever The pulmonary conditions were treated with antibiotics and in four patients with steroids as well

Fig 4 (upper views) represents the chest roentgenograms of patient No 6 at the beginning of mantle treatment There was considerable widening of the uperior mediastinum especially to the right with lymphomas in the right hilum The lymphomas were smaller at the end of the treatment (Fig 4 lower views) but there was still widening of the superior mediastinum The maximum absorbed dose in the lung parenchyma in the hilar regions corrected for the presence of lung tissue (SVAHN TAPPER 1970 and SVAHN TAPPER & LANDBERG 1971) had been 4 500 rad over 79 days and 31 fractions Roentgen examination of the chest 5 months after the beginning of mantle treatment revealed marked pulmonary parenchymal changes due to pneumonitis as well as additional pleural changes and fibrosis on the right side (Fig 5 upper views) The mediastinum with the trachea was displaced to the right The patient had cough and fever and received antibiotic therapy Roentgen examination 15 months after the beginning of mantle treatment disclosed further fibrosis (Fig 5 lower views) The pneumonitis in this patient was the most severe pulmonary reaction observed in the present material The patient improved and was then troubled by cough only on physical exertion Of the nine patients in whom roentgen examination had indicated pneumonitis six had been followed up for at least 10 months The last roentgen examination revealed considerable fibrosis in three patients only slight changes in two and normal conditions in one patient Two of the patients had neither symptoms nor signs of pneumonitis

As has been shown previously (SVAHN TAPPER 1970 and SVAHN TAPPER &



Fig 4 Frontal and lateral roentgenograms of patient No 6 *Upper views* At the beginning of mantle treatment Widening of superior mediastinum especially to the right with lymphomas in the right hilum *Lower views* At the end of mantle treatment Marked regression in the size of the lymphomas but persistent widening of the superior mediastinum

In no patient were there any symptoms of injury to the spinal cord nor to the cerebellum One patient (No 6) had moderate severe herpes zoster 3 months after the first mantle treatment One patient (No 8) maintained 10 months after the first treatment that some of her lower teeth had been injured by the therapy but this could not be objectively confirmed

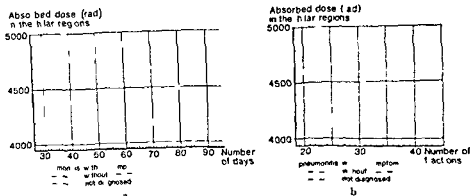


Fig. 6. Total maximum absorbed dose (rad) in the pulmonary parenchyma in the hilar region corrected for presence of lung tissue in ten patients given full mantle treatment (one patient excluded because of insufficient relevant dose measurements) in relation to the number of days (a) and to the number of fractions given (b).

by measurement of the exit absorbed dose in patients. These maximum absorbed doses in the hilar regions are given in Fig. 6 (patients Nos. 11 and 5 excluded because of too short observation time and too few measurements, respectively) in relation to the number of days (Fig. 6a) and the number of fractions given (*Fig. 6b*). They are presented as three types of reactions, namely roentgenologically demonstrated pneumonitis with or without symptoms and no diagnosed pneumonitis. The two patients in whom pneumonitis was not diagnosed had received treatment either over the longest period (94 days) or with the largest number of fractions (44), or had been given the lowest absorbed dose (4 200 rad). In the remaining eight patients, however, in whom the maximum absorbed dose in the hilar regions had been between 4 400 and 5 000 rad over 39 to 79 days and given in 20 to 33 fractions, no conclusions could be drawn about the type of fractionation and lung reaction. Nor was any correlation found between the presence of mediastinal lymphomas on roentgen examination before the treatment, or the histologic type of disease and the type of lung reaction, respectively. Roentgen examination revealed, however, pneumonitis in all three of the patients in whom treatment was given in one series, and two of these also had symptoms.

Of eight patients given split course treatment, two had neither symptoms nor signs of pneumonitis, whereas pneumonitis was roentgenologically demonstrated in six patients, three of whom also had symptoms.

Holsti & Vuorinen (1967) in an investigation of bronchial carcinoma reported that the incidence of radiation reactions in the lung within the dose range recorded as 3 100 to 4 000 R was smaller in the split course group than



Fig. 5. Frontal and lateral roentgenograms of patient No. 6. *Upper views:* Five months after the beginning of mantle treatment. Central pneumonitis as well as pleural changes and fibrosis on the right side; mediastinum with trachea displaced to the right. *Lower views:* Fifteen months after the beginning of mantle treatment. Further fibrosis.

LANDBERG 1971) the absorbed dose in the hilar regions owing to the presence of lung tissue is higher than that calculated on the assumption of homogeneous unit density tissue. The maximum absorbed dose in the hilar regions was calculated for lung tissue (SVAHN-TAPPER & LANDBERG 1971) by phantom studies and

In three of these patients (Nos 3 5 and 12) the values obtained before the treatments were normal and had not changed on examinations performed 12, 4 and 13 months respectively, after the treatment In a further three of the patients (Nos 6 8 and 10) there were slight restrictive changes at the last examinations made 15 10 and 7 months respectively after the treatment (the vital capacity decreased by 0 9 to 1 2 liter in two of them combined with a decrease in the maximal voluntary ventilation by 30 to 40 liter/minute) The last patient examined (No 4) had from the very beginning a lowered (1 liter) vital capacity which 11 months after the beginning of mantle treatment had not changed while the maximal voluntary ventilation had decreased by about 25 liter/minute

Except for the symptoms during the acute stage of irradiation pneumonitis the lung reactions resulted only in cough on exertion in some patients but never in subjective respiratory incapacity This corresponds well with the relatively moderate decrease in the spirometric values

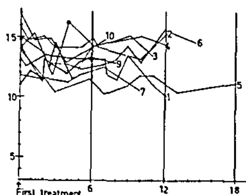
Depression of blood values Figs 7 and 8 give the pre per and post therapeutic hemoglobin values and respectively the erythrocyte leucocyte and thrombocyte counts in the nine patients with local disease who had received no treatment before they were given treatment according to the mantle technique All the four types of values generally fell during treatment but afterwards gradually rose to plateaux values only somewhat below the original values All patients were given iron and vitamin preparations during and after the mantle treatment Steroids were administered to four patients for pneumonitis No blood transfusions or cytostatics were given during the intervals shown in Figs 7 and 8 Patient No 5 was treated with an 'inverted Y shaped field technique started 6 months after the beginning of the mantle treatment but except for thrombocytopenia the blood values remained fairly constant

Acknowledgement

The authors are deeply indebted to Ass Prof I Nordenfelt for evaluating the electrocardiograms and spirograms

SUMMARY

A preliminary account of side effects and early results in twelve patients with Hodgkin s disease given radiotherapy with a mantle technique is presented Radiation pneumonitis developed in most patients Other side effects have been of less importance No further manifestations were observed in nine out of ten patients with clinically local disease followed up for on the average 12 months



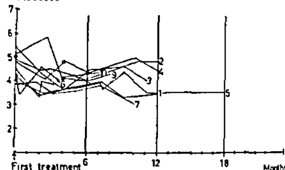
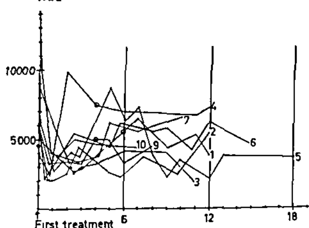


Fig 7 Hemoglobin values (left) and erythrocyte counts (right) at the beginning of mantle treatment and later in nine patients with local disease not treated earlier The small circles denote start of steroid treatment

in the group of patients given continuous treatment No precautions were taken in the present material to reduce the higher absorbed dose in the lung tissue of the hilar regions but the width of the field over part of the mediastinum is now diminished towards the end of treatment (SVAHN TAPPER & LANDBERG 1971) to make the absorbed dose in the hilar regions equal to the absorbed dose in the other parts of the target Furthermore, treatment is now always given as a split course

In seven of the patients, dynamic spirometry (including vital capacity, forced expiratory volume in one second and maximal voluntary ventilation) was performed before as well as 4 to 15 months after the beginning of mantle treatment



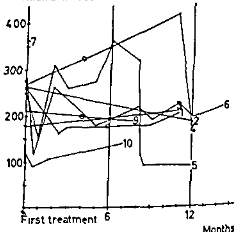


Fig 8 Leucocyte counts (left) and thrombocyte counts (right) at the beginning of mantle treatment and later in nine patients with local disease not treated earlier The small circles denote start of steroid treatment

FROM THE DEPARTMENT OF GYNAECOLOGY (DIRECTOR PROF H L KOTTMEIER)
RADIUMHEMMET STOCKHOLM SWEDEN

PROGESTERONE TREATMENT FOR LOCAL RECURRENCE AND METASTASES IN CARCINOMA CORPORIS UTERI

by

KARL KARLSTEDT

The treatment of carcinoma of the corpus uteri is usually surgical and the results are relatively good especially in young patients (KARLSTEDT 1968) The outcome is largely dependent on the extent of the growth its histology and the age of the patient (KARLSTEDT 1968, FURUHJELM 1969) Failure is usually due to the development of metastases or to local recurrence

KISTNER (1959) reported that large doses of progesterone may result in the disappearance of carcinoma in situ of the endometrium A favourable effect of this drug in pill form on lung metastases was reported by GYNNING (1961) KOTTMEIER (1954) introduced progesterone injections for metastases from corporeal carcinoma and reported that these disappeared or remained unchanged over a long period Since that time a series of patients with such *metastases* with or without recurrence of this form of carcinoma treated by progesterone has been collected in this series it has often been possible to conduct a fairly thorough analysis of the results of the treatment

Material This was restricted to patients in whom progesterone was the sole form of therapy so as to obtain indication of its effect those with local recurrence

Submitted for publication 3 April 1970

ZUSAMMENFASSUNG

Es wird ein vorläufiger Bericht über die Mantelbestrahlungsmethode bei zwölf Patienten mit Hodgkinscher Erkrankung einschliesslich der Resultate und ungewünschten Nebenwirkungen abgegeben. Strahlenpneumonie erfolgte bei den meisten Patienten und andere Nebenwirkungen waren von untergeordneter Bedeutung. Nach ungefähr einem Jahr hatten neun von zehn Patienten mit nur lokaler Erkrankung keinerlei aktive Symptome.

RÉSUMÉ

Compte rendu préliminaire des effets secondaires et des résultats précoces de l'irradiation par la technique en manteau chez douze malades atteints de maladie de Hodgkin. La plupart des malades ont eu une pneumopathie radiothérapique. Les autres effets secondaires ont été moins importants. Il n'y a pas eu d'autres manifestations chez neuf des dix malades présentant une atteinte cliniquement localisée et suivis en moyenne pendant 12 mois.

REFERENCES

FULLER, L. M. Results of intensive regional radiation therapy in the treatment of Hodgkin's disease and the malignant lymphomas of the head and neck. Amer. J. Roentgenol. 99 (1967) 340.

HOLSTI, L. R. and VUORINEN, P. Radiation reaction in the lung after continuous and split course megavoltage radiotherapy of bronchial carcinoma. Brit. J. Radiol. 40 (1967) 280.

JELLIFFE, A. M. The present place of radiotherapy in the cure of Hodgkin's disease. Clin. Radiol. 16 (1965) 274.

KAPLAN, H. S. The radical radiotherapy of regionally localized Hodgkin's disease. Radiology 78 (1962) 553.

— *Role of intensive radiotherapy in the management of Hodgkin's disease.* Cancer 19 (1966) 356.

— and ROSENBERG, S. A. Extended field radical radiotherapy in advanced Hodgkin's disease: short term results of 2 randomized clinical trials. Cancer Res. 26 (1966) 1268.

— — The treatment of Hodgkin's disease. Med. Clin. N. Amer. 50 (1966) 1591.

LUKES, R. J., BUTLER, J. J. and HICKS, E. B. Natural history of Hodgkin's disease as related to its pathologic picture. Cancer 19 (1966) 317.

NOBLER, M. P. Curative radiotherapy in the malignant lymphomas. Cancer 22 (1968) 752.

PETERS, M. V. A study of survivals in Hodgkin's disease treated radiologically. Amer. J. Roentgenol. 63 (1950) 299.

— *Prophylactic treatment of adjacent areas in Hodgkin's disease.* Cancer Res. 26 (1966) 1232.

— and MIDDLEMISS, K. C. H. A study of Hodgkin's disease treated by irradiation. Amer. J. Roentgenol. 79 (1958) 114.

SALZMAN, F. A., SMEDAL, M. I., WRIGHT, K. A. and TRUMP, J. G. Two MeV wide field irradiation of lymphoma. Amer. J. Roentgenol. 92 (1964) 124.

SMITHERS, D. A. Factors influencing survival in patients with Hodgkin's disease. Clin. Radiol. 20 (1969) 124.

SVAHN-TAPPER, G. Dosimetric studies of mantle fields in cobalt 60 therapy of malignant lymphomas. Acta radiol. Ther. Phys. Biol. 9 (1970) 190.

— and LANDBERG, T. *Mantle treatment of Hodgkin's disease with cobalt 60. Technique and dosimetry.* Acta radiol. Ther. Phys. Biol. 10 (1971) 33.

Table 2

Effect of progesterone therapy in carcinoma of the uterine corpus with metastases — Distribution by low and high doses and histologic grade

	Histologic grade				Total
	1	2	3	4	
Low dose					
Remission	0	1	0	0	1
No effect	0	8	3	0	11
High dose					
Remission	0	9	2	0	11
No effect	1	7	5	1	14

Table 3

Effect of progesterone therapy with respect to dose and histologic grade on lung metastases alone and when combined with metastases at other sites

	Histologic grade				Total
	1	2	3	4	
Low dose					
Remission	0	1	0	0	1
No effect	0	3	1	0	4
High dose					
Remission	0	7	0	0	7
No effect	1		4	0	7

The histologic grading of the primary tumour was based chiefly on the degree of differentiation (KARLSTEDT 1968). The findings were as follows (see also Table 2).

Histologic grade	1	2	3	4
No. of tumours	1	25	10	1

Results

Remission was recorded in 12 out of the 37 patients receiving progesterone (Table 2) and in 8 of the 19 of these with lung metastases (Table 3). In none of the patients with localized recurrence was there evidence of any beneficial effect of the drug.

Table 1

Progesterone therapy distribution in 37 cases of carcinoma of the uterine corpus with respect to form of primary treatment and clinical staging (1954—1968)

	Stages				Total
	I	II	III	IV	
Radiotherapy	13	8	4	4	29
Operation	8	0	0	0	8

or metastases in which radiotherapy and progesterone were combined were thus excluded The composition of the material with respect to previous treatment and clinical stage is presented in Table 1 Only patients given progesterone over a period of at least 4 months were included in the series Thus, those dying within this period and those whose general condition precluded the injections were omitted

There were 19 patients with lung metastases, eight of whom also had recurrences or metastases located elsewhere A further 18 patients had localized recurrences with or without metastases in organs other than the lung The metastases were verified by aspiration biopsy in three patients, the diagnosis was based on repeat roentgen examinations in the other patients with metastases alone All the local recurrences and lymph node metastases were verified histologically

Methods Progesterone was usually administered between 1954 and 1960 by injections of 25 mg doses three times a week With the introduction of concentrated gestagen it became possible to administer large doses, doses of from 250 mg three times a week to 1 000 mg daily have been given since 1961

The preparations used were Proluton Depot (17*a* hydroxy progesterone caproate) and in 3 patients SH 582 (17*a* hydroxy 19 norprogesterone caproate), 100 mg of the latter corresponds to 1 000 mg of Proluton Depot (Both preparations are manufactured by Schering A G) In the last few years it has been usual to give 1 000 mg daily for one week, followed by 500 mg three times a week over a long period In instances of remissions a maintenance dose of 250 to 500 mg a week has been administered

Remission was recorded when the metastases were no longer present roentgenologically, masses were not palpable at a subsequent examination or when lung metastases had remained stationary for more than one year, otherwise no remission was recorded

Discussion

Progesterone was first given to patients with lung metastases from carcinoma of the corpus uteri in 1950 by KELLEY et coll (1961), who observed a distinct regression of the changes in 6 patients of the 21 with advanced carcinoma of the body of the uterus or its recurrence Similar results have been published by BUDD WENTZ (1964) and BERGSJO (1965) Great interest in progesterone therapy in carcinoma of the corpus uteri was shown at the Fifth World Congress on Obstetrics and Gynaecology held in Sydney in 1967 when nine of the lectures dealt with this subject

NORDQVIST (1969) who has tried to elucidate the effect of progesterone in this type of carcinoma in experimental investigations has described a test for checking the sensitivity of the individual tumour to the hormone He ascribed the effect to the direct action of the hormone on the malignant cell and its process of nucleic acid synthesis

The absence of any reports of spontaneous regression of lung metastases from carcinoma of the body of the uterus in the literature suggests that spontaneous regression in this type of tumour does not occur (EVERSON & WARREN 1966)

Large doses of progesterone have been given since 1961 in the present series they have had a distinct effect on the lung metastases in some cases, chiefly in those of histologic grade 2

The withdrawal of the hormone therapy as soon as the roentgen examination has indicated that the lung metastases have disappeared would seem to be inadvisable The dose may however be reduced to a maintenance level say to 250 to 500 mg a week The risk associated with premature withdrawal is exemplified by a patient with probable lung metastases who prior to 1961 had been receiving low doses of progesterone The treatment was discontinued when the pulmonary changes had disappeared but a control carried out a year later revealed extensive and typical lung metastases

An autopsy series of patients dying of carcinoma of the corpus uteri (1947—54) included 90 patients with recurrences or metastases 18 of the metastases were in the lymph nodes 14 in the liver and 16 in the lungs This indicates the relative incidence of secondaries in the lungs Such metastases tend at first to produce only minor symptoms and often come to light only on routine roentgen examinations

SUMMARY

The results of the administration of progesterone as a depot preparation in a series of patients with carcinoma of the corpus uteri and pulmonary metastases are reported Progesterone should be used in all such conditions and might be tried in patients in whom the tumour has given rise to metastases at some other site

Table 4

Significance of age in progesterone therapy (high doses) in localized recurrence of carcinoma of the uterine corpus and metastases

Age	Lung metastases alone or with local recurrence		Metastases elsewhere than in the lungs	
	No. of cases	Remission	No. of cases	Remission
≤ 59 years	6	1	3	1
≥ 60 years	8	6	8	3

Table 5

Effect of progesterone therapy on metastases outside the lungs with or without localized recurrence — Distribution by low and high doses and histologic grade

	Histologic grade				Total
	1	2	3	4	
Low dose					
Remission	0	0	0	0	0
No effect	0	5	2	0	7
High dose					
Remission	0	2	2	0	4
No effect	0	5	1	1	7

The effect of the therapy in relation to the degree of differentiation of the tumour is presented in Table 2. Remission was recorded in 10 of the 25 patients assigned to histologic grade 2 and in 2 of the 10 with grade 3 tumour. The effect of the progesterone seems to have been dependent in some measure on the dose, *remission was observed in 11 of the 25 patients* receiving high doses but in only 1 out of the 12 patients with low doses.

In 3 patients with histologically verified lung metastases that disappeared after the hormone therapy, the survival times were 9.8, 7.5 and 3.5 years, respectively.

So far as age is concerned the treatment was most effective in patients over 60 with pulmonary metastases (Table 4). The treatment was never accompanied by serious complications, *in a few instances the patient developed* a cough in direct connection with the injection.

FROM RADIUMHEMMET (DIRECTOR PROF J EINHORN), THE DEPARTMENT OF OPHTHALMOLOGY (DIRECTOR PROF G KARPE), KAROLINSKA SJUKHUSET AND THE DEPARTMENT OF CLINICAL RADIOPHYSICS (DIRECTOR PROF R WALSTAM) NATIONAL INSTITUTE OF RADIATION PROTECTION, STOCKHOLM, SWEDEN

OPHTHALMOLOGIC OBSERVATIONS ON LONG TERM SURVIVORS AFTER RADIOTHERAPY FOR NASOPHARYNGEAL TUMOURS

by

A DE SCHRYVER, LILLEMOR WACHTMEISTER and I BARYD

The late radiation effects on a variety of anatomic structures both intra and extracranial may be evaluated in long term survivors after radiation treatment for malignant nasopharyngeal tumours Because of the position of the naso pharynx practically at the centre of the head it is impossible for the therapist completely to avoid neighbouring structures such as the eye or the medulla Moreover because of the tendency for these tumours to invade the base of the skull it is customary to include the floor of the middle cranial fossa in the target area indeed it may be expected that several structures at the base of the brain such as the lower part of the temporal lobes some of the anterior cranial nerves the chiasma and the pituitary gland will be exposed to considerable doses of radiation

An evaluation of the tolerance of these tissues to ionizing radiation in man presents a complex problem when radiotherapy has been given for primary intracranial disease for example pituitary adenoma or intracranial tumour It may

Submitted for publication 30 April 1970

ZUSAMMENFASSUNG

Es wird über den Wert der Anlage von Depots von Progesteron bei einer Serie von Patienten mit Carcinom des Corpus uteri mit Lungenmetastasen berichtet. Progesteron sollte in allen solchen Fällen gegeben werden und sollte in Fällen, wo die Metastasen andere Körpergegenden befallen, versucht werden.

RÉSUMÉ

L'auteur présente les résultats de l'administration de progestérone sous forme de dépôt chez une série de malades atteintes de cancer du corps de l'utérus avec métastases pulmonaires. On devrait utiliser la progestérone dans tous ces cas et on devrait l'essayer chez les malades dont la tumeur a donné naissance à des métastases situées ailleurs que dans le poumon.

REFERENCES

BERGSJÖ P.: Progesterone and progestational compounds in the treatment of advanced endometrial carcinoma. Acta endocr. (Kbh.) 49 (1965), 412.
BUDD WENTZ W.: Effect of a progestational agent on endometrial cancer. Obstet. Gynec. 24 (1964), 370.
EVERSON T. C. and WARREN H. C.: Spontaneous regression of cancer. W. B. Saunders, Philadelphia 1966.
FURUHJELM M.: *Cancer corporis uteri (In Swedish.)* Nord. Med. 81 (1969), 635.
GUNNING L. and CLAESSON L.: Progesteronbehandling av lungmetastaser vid gynekologisk cancer — några instruktiva fall. (In Swedish.) Nord. Med. 65 (1961), 571.
INGELMAN-SUNDBERG A.: *Some aspects on the treatment of carcinoma corporis uteri.* Edezioni Scientifiche Salpietra, Firenze 1962.
KARLSTEDT K.: Carcinoma of the uterine corpus. Factors bearing on the curability. Acta radiol. *(1968) Suppl. No. 282.*
KELLEY R. M. and BAKER W. H.: Progestational agents in the treatment of carcinoma of the endometrium. New Engl. J. Med. 264 (1961), 216.
KISTNER R. W. and GRIFFITHS C. T.: *Use of progestational agents in the management of* metastatic carcinoma of the endometrium. *In:* Chemotherapy of gynecologic cancer. Edited by E. D. Hreshcyn. Harper Row Publishers, New York 1968.
NORDQVIST S.: *Hormonal responsiveness of human endometrial carcinoma studied in vitro* and in vivo. Studentlitteratur, Lund 1969.

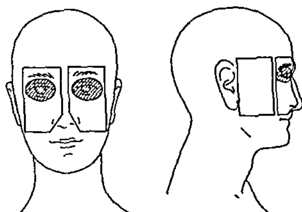


Fig 1 The limits of the anterior and lateral fields

fields the latter deflected about 15° inwards The radiation energy was approximately 190 kVp with a HVL of 1 mm Cu the FSD being 50 cm The field limits were as follows (Fig 1) (1) Lateral field Superior limit corresponding to the upper border of the pinna, posterior limit immediately anterior to the tragus, anterior limit about 1 cm behind the lateral border of the orbit, inferior limit about 1 cm above the angle of the mandible (2) Anterior field Superior limit including the eyebrow (which, however was shielded) inferior limit middle of upper lip medial limit included the ala nasi lateral limit the lateral border of the orbit The eye was protected by an oval lead shield measuring about 45 × 30 × 3 mm

The target always included the base of the skull the immediately contiguous parts of the brain stem in the middle cranial fossa, and the lower part of the temporal lobes The exposure in most of the patients was between 2 400 and 3 000 R per field (skin exposure) depending on the pathology and the regression of the tumour during the treatment The entire course was given in 20 to 40 days the estimated tumour dose ranging roughly from 5 000 to 6 000 rad If the tumour was still visible or possibly had not completely disappeared 6 to 8 weeks after completion of the roentgen course a 50 mg radium source filtered by 4 mm Al was applied locally for between 3 and 8 hours If treatment had to be given to both sides of the nasopharyngeal cavity an application was made on 2 consecutive days

This investigation was not concerned with the value of the treatment method as such All but one of the patients were treated at least 10 years ago since when supervoltage techniques have been introduced for nasopharyngeal tumours

be difficult, if not impossible in such cases, to tell whether any changes are attributable to the underlying condition or to late effects of radiation.

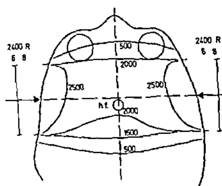
The aim of the present investigation was to examine the possibility of late radiation induced lesions of the optic nerve. However, because of the vicinity of the eyeball itself to the radiation focus in the nasopharynx and hence the likelihood of significant exposure, the lens and the choroidoretinal tunic were also included in the examination. This was in spite of the fact that as a result of protective measures, the doses were expected to be low and postirradiation changes of the lens have been well documented (3, 5, 8, 11, 17, 18, 23).

Material and Methods

During the 25 year period 1937—1962 approximately 650 cases of malignant nasopharyngeal tumours (mainly poorly differentiated carcinomas and reticulum cell sarcomas) were treated by full course radiotherapy. All the patients were followed up at least once a year, indefinitely. The crude 5 year survival rate was about 30 % for the tumour group as a whole. Among those living at the time of the present investigation were 80 patients who had survived for at least 5 years, including 58 who had lived for 10 years or more. Of this latter group 50 patients were called for special ophthalmologic control, the remaining 8 patients being either too old or in poor general condition. Twenty nine of the 50 patients presented for examination, one patient with a survival of only 7 years was also included, making a total of 30 (9 women and 21 men). Their ages at the time of the investigation ranged from 43 to 77, mean 61, years and at the time of treatment from 16 to 59, mean 42, years. As regards the representativeness of the group, one of the most frequent reasons given for not attending the examination was that the patient was doing well and working. Admission to hospital for about a week (other tests were run simultaneously) would in some instances have resulted in financial loss. Most of the patients with any complaints at all were eager to be examined. It would therefore seem that there was no over-representation of normal or symptom free subjects in the material.

Of the patients examined, 5 had a history of hypertension. None had diabetes mellitus, nor had any of them ever been treated with steroids or miotics. Eight patients had a history of ophthalmologic disease: corneal ulcer in 3, iritis in 2, contusions in 2 and possible vitreous haemorrhage in 1 patient. In none of these patients was there a time relationship between the eye condition and the radiation treatment; in fact, in most of them an obvious, purely ophthalmologic cause existed.

The treatment method used was basically the same for all the patients and may briefly be described as a 4 field technique with two lateral and two anteriormalar



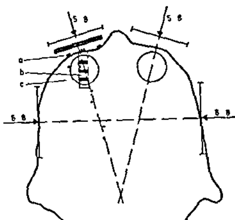


Fig 3

Fig 4

Fig 3 Example of computed dose distribution in plane A (lateral field contributions only) h f = hypophyseal fossa.

Fig 4 Cross section through the skull phantom in plane A a) LiF rods on surface immediately below lead shield b) Cylindrical cavity containing 3 sets of 4 to 5 LiF disks each Residual space filled with perspex blocks c) Holes for TLD rods

In each case a dose distribution was computed at eye level using standard isodose diagrams corresponding to a HVL of 1 0 mm Cu (FSD = 50 cm) As the optic chiasma and the eyeball are situated at this level lying either entirely within (for the latter) or close to (for the former) the region of protection produced by the lead eye shields the isodose plotting was greatly complicated To simplify the situation only the dose delivered by the lateral unshielded fields (Fig 3) was considered and to this was added a theoretical fraction of the anterior surface dose based on phantom measurements behind lead (see below) It was assumed that both the eye and the optic chiasma were entirely shielded but as stated above this was not in fact so The irradiation at that time was however performed without any head immobilizing device and slight movements might have brought the chiasma within the cone of protection produced by the eye shield It was therefore considered that the above assumption would provide a lower limit for the chiasma dose

The total contribution of the two anterior fields was for the lens approximately 14 % for the posterior pole of the eyeball 17 % and for the chiasma 25 % of the surface dose All the tissue doses are expressed in rad Corrections of — 7 % each were made for bone absorption (4 mm) for the lateral fields

Phantom measurements Measurements were made in a water and in an anatomic skull phantom The dose measurements in the water filled perspex tank

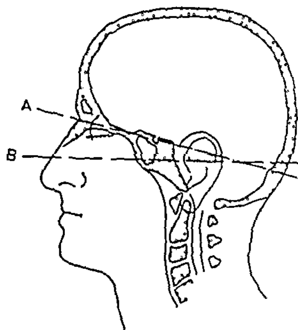


Fig. 2. Sagittal section. A the plane of the isodose plotting and B the approximate direction of the a. p. beams.

Estimation of the absorbed radiation dose

Theoretical reconstruction of dose distribution. When a preliminary series of 10 patients had been examined an attempt was made in all the subsequent 20 patients to reconstruct the dose distribution for each patient. An anatomic contour that intersected the base of the skull approximately at the sella turcica was obtained at eye level (Fig. 2). Epilation and skin atrophy often enabled the fields to be easily reproduced and photographs of the patient taken during treatment and showing the skin reaction were sometimes available. Simulator roentgenograms of all the fields, that enabled the actual treatment conditions to be reconstructed and the exposed structures to be located exactly, were obtained for all the patients. Films for the anterior fields were obtained both with and without an eye shield. It proved that the chiasma had always been included in the lateral beams and usually in the a. p. beams as well. The site of the optic chiasma on the sphenoid body was evident in the simulator films near the inner limit of the field, close to the border of the eye shield.

The following values for certain anatomic measurements were assumed for the purpose of this investigation: thickness of the eyelid 2 mm (mean of authors' measurements), cornea 0.6 mm (WOLFF 1961), anterior chamber 3.5 to 4 mm (JANSSON 1963) and lens 3.5 to 4.2 mm (JANSSON), the axial diameter of the eyeball 23 mm (females) and 24 mm (males) (JANSSON). The distance between the surface of the closed eyelid to the lens equator plane was thus about 8 to 9 mm. The distance to the posterior pole of the retina was approximately 24 mm

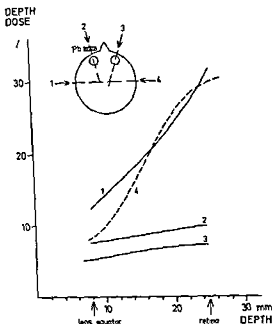


Fig 5 Contributions of the 4 fields to one eye as measured in an anatomic phantom by TL dosimetry The lens is at about 8—9 mm depth the retina at about 25 mm

to the lens and the retina and 100 rad to the optic nerves and were regarded as negligible They are not included in the dose figures recorded in this paper

LiF rods were placed on the surface of the anatomic phantom immediately behind the shield and LiF disks at progressive depths along the axis of the lens in order to determine the dose gradient in the first 30 mm behind the eye shield (Fig 4) The total doses contributed by the two anterior fields to each lens and retina were approximately 14 and 17 % of the nominal surface dose (Table 1 and Fig 5)

The largest contribution to the retina came from the lateral field, the projection of its anterior margin being almost tangential to the posterior pole of the eye The calculated dose distributions in plane A (Fig 3) were moreover verified by LiF rod measurements at a number of points

Estimation of the radiation dose at the level of the optic chiasma was particularly delicate because of its proximity to the borders of the region of protection produced by the eye shields As these shields covered almost the entire width of the anterior field (Fig 1) straightforward 4 field isodose plotting was considered unpractical and instead direct phantom measurements were regarded as being the only method likely to give dependable figures for the anterior field contributions (Measurements of depth doses for the lateral field indicated acceptable agreement with the values obtained diagrammatically)

Table 1

Approximative cumulative depth doses (as percentage of nominal surface dose) in lens and retina

Field	Depth dose	
	Lens	Retina
Anterior	14 %	17 %
Lateral	20 %	60 %

(30 × 30 × 40 cm) were recorded with a Siemens Sondenfingerhutkammer with a Philips ionization chamber as monitoring instrument. Some measurements required a small chamber with an external diameter of only 7 mm (BENNER et coll. 1959). The anatomic phantom consisted of a natural skull on which the external soft tissue structures were modelled in Mix D, a tissue equivalent compound (JONES & RAINE 1949); it has been demonstrated by, among others, DAHL & VIKTERLOF (1958) that this paraffin mixture has a satisfactory radiophysic water equivalence. The intracranial cavity was filled with the same material, in which narrow holes could easily be drilled to receive either small Sievert condenser chambers (SIEVERT 1932) or three types of thermoluminescence dosimeters (TLD), namely, lithium borate ($Li_2B_4O_7$: Mn) and lithium fluoride (LiF) teflon rods measuring 1 × 6 mm, and lithium fluoride disks measuring 0.5 × 8 mm.

The thermoluminescence dosimeters were calibrated against ^{60}Co gamma radiation, and their energy dependence for the relevant roentgen energy (190 kV) was determined. Before reading (on an instrument manufactured by Controls for Radiation, Inc.), the lithium fluoride dosimeters were brought to zero by exposing them for 15 minutes at 300° C, followed by 24 hours at 80° C. The lithium borate rods needed only 30 minutes at 300° C.

The irradiation conditions were similar to those for the clinical treatments (190 kV roentgen rays, 0.5 mm Cu + 1.0 mm Al filtration, HVL 1 mm Cu, FSD 50 cm). The field sizes, 5 × 8 cm and 6 × 8 cm for the anterior and lateral fields respectively, matched the above mentioned anatomic landmarks. The positions of the beams were checked on the simulator. The eye was protected by an oval, 3 mm thick lead shield during irradiation of the anterior fields. The doses were measured and computed in a plane passing through the eyeballs and the sella turcica (Fig. 2, plane A). The estimated dose contributions from the radium applicators to the target areas probably never exceeded 50 rad

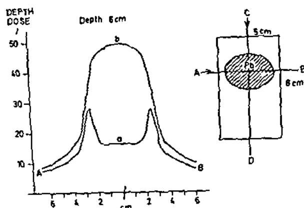


Fig 7 Recording of the radiation intensity (percentage of surface value) at 6 cm depth as a function of chamber position (movement direction AB)

of the protected zone but rose sharply to a maximum as the chamber moved over the boundary (from 16 to 27 % in the example given)

As these results indicate the absorbed doses were subject to important variations in the marginal zone of the cone of protection produced by the eye shield, and it was therefore decided to accept as a lower limit the minimum dose obtained during the measurements behind the lead protector i e 12 5 % × 2 = 25 % (Table 2) In each case this value was added to the lateral field contribution determined from the isodose reconstructions to obtain the minimum doses The estimated maxima were obtained by adding to the same lateral field contributions a fraction indicated by curve b in Fig 7 for each case where the chiasma region could be seen outside the lead shield (the vast majority) Although these computed maxima were often considerably higher they were probably closer to the true doses than were the minimum figures

Ophthalmologic examination

Three distinctive anatomic and functional units associated with the sense of vision are to some degree exposed to radiation in the treatment of malignant nasopharyngeal tumours by the above mentioned technique these are the optical media of the eye the receptor system in the retina and the afferent pathway of the optic nerve (The quadrigeminal and occipital centres are normally not included in the radiation zone) The patients in this investigation were therefore examined for possible damage at the three above mentioned levels the media the choroidoretinal tunic and the optic nerve

The following examinations were carried out in all patients Visual acuity, tonometry according to Schiotz slit lamp microscopy transillumination of the

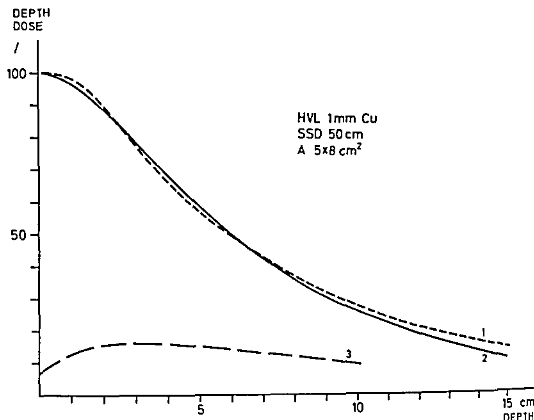


Fig 6 Depth dose curve (3) behind the centre of a 3 mm lead eye shield in a water phantom Normal curves (1) (authors measurement) and (2) (according to Brit J Radiol Suppl No 10) given for comparison

The first step was to determine in a water phantom the depth dose curve behind the typical lead eye shield with a Siemens Sondenfingerhutkammer As the dose was fairly constant over a wide range (Fig 6) the depth of the shielded structure relative to the anterior surface of the skull was of minor importance However, since the simulator films indicated that the chiasma lay situated mostly outside the protected zone, more important were the depth dose variations in a plane perpendicular to the beam axis at the approximate depth of the chiasma This was examined in a water phantom in which a small ionization chamber (BENNER et coll 1959) coupled to an X—Y registering device automatically scanned the radiation intensity perpendicular to the incident beam Measurements were performed at three depths (5, 6 and 7 cm) and in two perpendicular directions (AB and CD in Fig 7) Measurements were made with (curve a) and without (curve b) a lead shield An example of a measurement recorded at a depth of 6 cm appears in Fig 7 The dose was relatively constant over most

region and 7 in the perinuclear subcapsular region Purely cortical opacities (granulae and pokes) were observed in 6 patients 2 of whom also displayed posterior subcapsular changes one with perinuclear subcapsular changes and the other with anterior subcapsular vacuoles and posterior subcapsular opacities One patient had anterior and another posterior subcapsular vacuoles

The fundi The lenses were so opacified in one patient that finer details could not be seen at ophthalmoscopy In another patient the left lens was opacified to such a degree that ophthalmoscopy of only the right eye was possible Of the remaining 29 patients including this last one, 5 presented retinal changes characterized by small round haemorrhages and micro-aneurysms mainly in the macula Two of these 5 patients were, or had been suffering from hypertension Extensive haemorrhage exudate and pigmentation were present in one patient who had been suffering from hypertension but whose blood pressure had fallen without any treatment within normal limits Fundus hypertonicus I and II was evident in 4, arterio clerotic changes in 7 and peripapillary atrophy (without myopia) in 3 patients The maculae were stippled with fine glistering dots and small yellowish atrophic patches in 14 patients

The perimetry No changes characteri tic of optic nerve lesions were present A bilateral concentrically contracted visual field without hemianopsy or central scotoma was evident in one patient The patient had moderate myopia (—8 0) with impaired vision (right eye = 0 4 and left eye = 0 5 after correction) and collaborated poorly Another patient pre ented with a concentric contraction of the left visual field but even here vision was impaired (left eye = 0 7 after correction) and collaboration poor In another four patients there was relative contraction of the upper part of the fields tested with a small and dimly lit object (0 33 0 10 1/4 mm) as in vascular conditions Both eyes were affected in two of them and left eye only in the other two

Vision Twenty two of the 30 patients examined had normal visual acuity after correction of any refractive errors and in 8 patients vision was impaired Of these one patient presented with corneal scars of traumatic origin and another had hyperopia and in childhood probably strabismus In the remaining 6 patients the impaired vision was due to lens opacity — 2 with cortical 2 with posterior subcapsular 1 with posterior and peripheral cortical (in this patient however, a moderate myopia may have been a contributing cause) and 1 with perinuclear subcapsular opacity

Intra ocular pressure This was normal in all but one of the 30 patients (a moderately increased pre sure was recorded in this patient and bilateral glaucoma simplex was subsequently treated)

Colour perception — Eight of the 30 patients including one female had defective colour perception — congenital in 3 and of obscure origin in 3 the

Table 2

Relative depth dose in the region of the optic chiasma

Field	Relative depth dose values			
	Condenser chamber	TLD	Siemens chamber	Isodose diagram*
Anterior**	13 %	12 %	12.5 %	—
Lateral	43 %	44 %	—	42 %

* Corrected for bone absorption

** It is assumed that the region of the chiasma is completely shielded

optic media, and ophthalmoscopy after dilating the pupil with Mydriacyl, perimetry according to Goldmann and colour vision tests with pseudoisochromatic plates according to Boström & Kugelberg and Boström II (4,15). ERG was recorded by the Karpe method (14) in one patient and an adaptation curve was obtained; in a few other cases photographs of the lens (direct transillumination) and fundus were taken.

Dose calculations are not available for 10 of the patients. However, as they did not constitute a selected group, either clinically or as regards the treatment technique, their data were included in the investigation.

Results

Estimated absorbed radiation doses

Lens and retina. The doses calculated and checked by the techniques described above ranged for the lens from 600 rad in 5 weeks to 1 100 rad in 4 weeks. The figures were of course higher for the posterior pole of the eye, corresponding to the central part of the retina. Moreover, at this level an attempt was made to determine a dose range; not unexpectedly these ranges varied quite widely — from 100 to 1 800 rad. Among the lowest figures recorded lie 1 300 to 1 800 rad, and among the highest ones 3 200 to 3 500 rad.

Optic chiasma. The minimum values ranged from 1 800 to 4 300 rad, and the maximum ones from 2 000 to 4 900 rad. Moreover, at least 3 cases had maximum doses of between 4 400 and 4 900 rad.

Ophthalmologic data

The media. Pathologic changes of some sort were observed in one or both lenses in 25 of the 30 patients. Ten had opacities in the posterior subcapsular

Ten of the present 25 patients presented posterior subcapsular opacities of the type associated with radiation cataract (COGAN et coll 1952) this would be almost twice as many as would be expected in a normal population with the approximate age distribution of the present series A further 7 patients had disseminated small punctiform opacities with a perinuclear subcapsular distribution such as have been reported in radiation cataract (8) This type of opacity which was not mentioned by CINOTTI & PATTI (1968) can be differentiated clinically from the flocculent whitish nuclear or subcapsular changes, located for the most part posteriorly evident in diabetes Finally 2 patients had anterior subcapsular vacuoles such as those observed by AXELSSON & HOLMBERG (1966) after treatment with miotics however none of the patients had received such drugs and moreover this type of change has been known to develop after radiation (8) In summary 19 of the 30 patients presented with alterations consistent with radiation induced cataract and it would thus seem likely that a number of the changes discovered in their lenses were in fact, due to the irradiation treatment This is the more probable as the calculated lens doses (600 to 1 100 rad) all fall within a range known to be potentially cataractogenic (MERRIAM & FOCHT 1957) However, to judge from the results of CINOTTI & PATTI (1968) the alterations in some of these 19 patients might well have been of a purely senile type

Functionally almost all the observed lens changes consistent with radiation induced cataract were benign in that they were small, stationary and affected vision only slightly if at all This is in agreement with the observations of several other investigators (QVIST & ZACHAU CHRISTIANSEN 1959 MERRIAM & FOCHT 1957 MILLER et coll 1967) According to MERRIAM & FOCHT progressive cataracts resulting in complete opacification of the lens and corresponding loss of vision would be expected mainly with doses above 1 000 rad although might occasionally occur at lower dose levels In this series with none of the estimated lens doses exceeding 1 100 rad only one patient had lens changes of the radiation induced type (a dense posterior subcapsular discoid opacity) that had resulted in markedly impaired vision (0 3 to 0 4 for the more affected eye) The dose absorbed by the lens was estimated at 1 100 rad Two further patients in this series presented with a considerable loss of vision (0 5 or less) but the lens changes were of a more senile type Moreover moderately severe myopia (—8) may have contributed to the loss of vision in one of them

Cataracts occurred in about 61 % of the patients with estimated lens exposures of 550 to 1 150 R in the series of MERRIAM & FOCHT (1957) The corresponding figure for the present series with ophthalmologic appearances as in radiation cataract was 63 % for estimated lens doses of 600 to 1 100 rad

The choroidoretinal tunic Although the retina is more radio resistant than the

remaining 2 patients, including the woman, collaborated poorly owing to advanced age.

An electroretinogram (KARPE 1945), recorded in one patient with extensive fundus lesions, presented normal values. The adaptation curve was also normal.

Discussion

As in all such investigations, the dosimetry was based on reconstructions that are inevitably in some measure artificial. While it is probably safe to say that the figures for the doses administered are accurate to within 10 %, the margin of error for the relevant geometric factors cannot be so exactly determined. Slight day to day variations in the positioning of the patient may have resulted in a depth dose distribution somewhat different from the reconstructed one. As the structures investigated were situated in zones where relatively steep dose gradients might be expected, the doses may have been significantly influenced by small variations. Account was taken of this whenever possible by specifying an estimated dose range instead of a single value. All the calculations were made without knowledge of the clinical findings.

Lens. The radiosensitivity of the lens is well established, both experimentally and clinically, and comprehensive reviews of the literature on the subject have been given by POPPE (1942), HAM (1953) and PISTOLESI (1959). It is now generally accepted that 400 R can be considered as a threshold dose, at least in the adult and for roentgen rays, and when fractionated over three or more weeks, while 1 200 R will invariably induce some degree of radiation cataract (MERRIAM & FOCHT 1957). Although this investigation was not primarily concerned with radiation induced lens changes, they were none the less carefully studied. Radiation cataract has been extensively investigated both in animals and clinically. Initially, small opacities appear subcapsularly in the region of the posterior horizontal suture; these eventually acquire a 'doughnut' form, evident in the slit lamp beam as a bivalve configuration. Large vacuoles and polychromatic cysts located subcapsularly in the posterior cortex as well as thin granular and feather-like formations may develop. Gradually, a dense discoid opacity is formed in the posterior pole. An anterior subcapsular haze may appear, eventually together with vacuoles. Finally, the lens is completely opacified (18).

Lens changes of some sort were discovered in 25 of the 30 patients. CINOTTI & PATTI (1968) in an examination of a 'normal' population of 177 persons with about the same median age as the present group of patients and with no history of diabetes, glaucoma or congenital lens opacity observed posterior subcapsular opacities in about 19 %. There were no sex differences.

et coll (1968) who moreover, concluded from their clinical data that the radiosensitivity of the human retina was comparable to that of the rabbit retina Only after single doses of at least 5 000 rad may serious and probably irreversible damage of the receptor and bipolar cells of the retina be expected Admittedly these findings have no bearing on possible late secondary changes resulting from radiation induced vascular damage as indeed were most of the changes in the present cries Even in the more severe cases vision would hardly be affected The human retina would appear to tolerate doses up to 3 000 to 3 500 rad if fractionated over 4 to 5 weeks and although hypertensive vascular changes were sometimes present

The optic nerve Little is known about the radiosensitivity of the optic nerve As reported by BIEGEL the results of earlier investigations (before the thirties) are conflicting probably owing at least in some degree to dosimetry problems In this author s more recent experimental work (1955) in the rabbit, exposure of the optic nerve to 23 MeV roentgen rays in doses of up to 4 500 R and to the same doses of 17 and 19 MeV electrons failed to produce histologic evidence of radiation damage Despite the general agreement on the relative radio-resistance of the optic nerve (3 22) actual data in man are scarce CLAUS et coll (1968) described optic nerve damage in 8 out of 25 irradiated cases However the total dose to the nerves was 6 000 to 8 000 R and moreover, in at least 5 of the ca es other local factors such as tumour growth or ocular complications (glau coma inflammation) were either wholly or at least partially responsible for the observed optical atrophy

No damage to the optic nerves detectable by perimetry was recorded in any case of the present series although in at least 3 the dose was not less than 4 400 rad that is if it assumed that the upper limit of the calculated dose ranges is the more realistic In none of the cases with impaired vision was this due to an optic nerve lesion but to changes in the media (plus one patient of hyperopia and probably strabismus in childhood) Even the 3 patients which chiasma doses of 4 400 rad or more had both normal vision and normal visual fields

The figure of 8 out of 30 patients for defective colour perception is more than three times the expected frequency (about 8 % in males and 1 % in females) The history in 3 patients proved the anomaly to be congenital and in 2 the situation was dubious because of poor collaboration from the elderly patients In 2 of the remaining 3 patients the absorbed dose in the chiasma was estimated at about 4 400 rad and in the third patient it was unknown While defective colour perception cannot confidently be ascribed to the absorbed radiation it would seem no less difficult to rule out some form of damage to the optic nerve

lens a number of experimental observations have indicated that at least some elements of the retina may be seriously damaged by relatively moderate doses in the range of 2 000 rad (CIBIS et coll. 1955). Recent investigations in the rabbit carried out by DEVI et coll. (1968) and LOMMATZSCH et coll. (1968) have disclosed the effect of different radiation doses on the electroretinogram (ERG) in experiments covering a few days up to three weeks.

The conditions under which many of these observations were made preclude them being always directly applicable to clinical situations (where large single doses of radiation are the exception rather than the rule). It is however evident that the possibility of radiation induced damage to the retina should be borne in mind whenever this has been exposed to more than 2 000 rad.

Both the macula and the retinal vessels were entirely normal in 11 patients of this series. At least one type of change (microaneurysm, haemorrhage, atrophy, the presence of small, glistering dots) was present in 18 patients. Refined ophthalmoscopy was impossible in one patient. To examine whether these alterations might be in any way related to the amount of absorbed radiation, the group of 20 patients where dose reconstructions were available was divided roughly and quite arbitrarily into those receiving less and those receiving more than 2 500 rad on the posterior third of the eyeball (6 and 14 patients, respectively). In the "low dose" group the findings were quite normal in 4 out of 6 patients, they were difficult to assess in one but no gross changes were evident, while in one atrophic changes were present in both maculae. In the other 14 patients the maximum dose to the retina was estimated to be higher than 2 500 rad, and all with abnormal findings except one belonged to this "high dose" group (11 out of 14).

The extent to which the changes observed may be ascribed to radiation is difficult to decide. As PERPERS TAYLOR et coll. (1965) stated, all types of radiation induced alterations in the choroid and retina may occasionally occur in the elderly as purely senile changes. It was therefore impossible to attribute the changes observed to the radiation exposure with any degree of confidence and in the hypertensive patients they may have had a purely vascular origin. However, as all but one of the changes were observed above a certain dose level, the radiation was probably of etiologic importance. Furthermore, one of the patients in whom the retina was apparently exposed to one of the highest doses (3 400 rad), presented the most intense pathologic changes (haemorrhage, exudate and pigmentation). The fact that the electroretinographic response and adaptation curve were normal does not exclude the possibility that the lesions were due to radiation damage. In a recent experimental investigation of the rabbit retina, LOMMATZSCH et coll. (1968) reported that less than 5 000 rad ^{60}Co gamma radiation in one single dose would not produce appreciable lasting changes in the ERG, at least in short term observations. Similar findings were reported by DEVI

4 BOSTROM C G Fargsinneskontrollens organisation (In Swedish) Svenska Lak Tidn 41 (1944) 2885
5 CIBIS P A NOELL W K and EICHEL B Ocular effects produced by high intensity X radiation Arch Ophthal 53 (1955) 651
6 CINOTTI A A and PATTI J C Lens abnormalities in an aging population of nonglaucomatous patients Amer J Ophthal 65 (1968) 25
7 CLAUS H G DIETHELM L und CULLMANN B Der Einfluss einer hochdosierten Gammastrahlung auf das menschliche Auge Strahlentherapie 136 (1968) 395
8 COGAN D G DONALDSON D D and REESE A B Clinical and pathological characteristics of radiation cataract Arch Ophthal 47 (1952) 55
9 DAHL O and VIKTERLOF K J Dose distributions in arc therapy in the 200 to 250 kV range Acta radiol (1958) Suppl No 171
10 DEVI S K RILEY E F and BURNS C A Electroretinographic responses of the rabbit after x irradiation Invest Ophthal 7 (1968) 219
11 HAM JR W T Radiation cataract a review Arch Ophthal 50 (1953) 618
12 JANSSON F Measurements of intraocular distances by ultrasound Acta ophthal (1963) Suppl No 74
13 JONES D E A and RAINE H C Letter to the Editor Brit J Radiol 22 (1949) 549
14 KARPE G The basis of clinical electroretinography Acta ophthal (1945) Suppl No 24
15 KUGELBERG I De nya svenska fargsinnestavlorna (In Swedish) Svenska Lak Tidn 41 (1944) 2898
16 LOMMATZSCH P FURST G und ULRICH W D Vergleichende morphologische und funktionelle (ERG) Untersuchungen an der Retina des Kaninchens nach Einwirkung von Gammastrahlen (^{60}Co) und hochenergetischen Elektronen Albrecht v Graefes Arch Ophthal 175 (1968) 34
17 MERRIAM JR G R and FOCHT E F A clinical study of radiation cataracts and the relationship to dose Amer J Roentgenol 77 (1957) 759
18 — — Clinical and experimental study of effect of single and divided doses of radiation on cataract production Trans Amer ophthal Soc 60 (1962) 35
19 MILLER R J FUJINO T and NEFZGER M Lens findings in atomic bomb survivors Arch Ophthal 78 (1967) 697
20 NOTTER G WALSTAM R and WIKHOLM L Radiation induced cataracts after radium therapy in children *In* Proceedings of the first Nordic Radiation Protection Conference Acta radiol (1966) Suppl No 254 p 87
21 PERRERS TAYLOR M BRINKLEY D and REYNOLDS T Choroido retinal damage as a complication of radiotherapy Acta radiol Ther Phys Biol 3 (1965) 431
22 PISTOLESI G F Radiation injury of ocular structures comprehensive review Quad Radiol 24 (1959) 471
23 POPPE E Experimental investigations of the effects of roentgenrays on the eye Jacob Dybwad Oslo 1942
24 QVIST C F and ZACHAU CHRISTIANSEN B Radiation cataract following fractionated radium therapy in childhood Acta radiol 51 (1959) 207
25 SIEVERT R M Eine Methode zur Messung von Rontgen Radium und Ultrastrahlung nebst einige Untersuchun en uber die Anwendbarkeit derselben in der Physik und der Medizin Acta radiol (1932) Suppl No 14
26 WOLFF E Pathology of the eye Cassel & Co London 1961

Acknowledgements

The location of the optic chiasma, in particular, was carefully reviewed by Curt Lagergren and Paul Edholm, both at the Department of Diagnostic Radiology, Karolinska Sjukhuset, to whom the authors wish to express their gratitude.

SUMMARY

Thirty patients who had received radiotherapy seven to thirty years previously for nasopharyngeal tumours were examined ophthalmologically for late radiation changes. Opacities in the lens were present in 25 of the patients, in 19 with characteristics similar to those in radiation cataract. Choroidoretinal changes were evident in 1 of the 6 patients for whom the estimated absorbed dose had been less than 2 500 rad over 3 to 5 weeks and in 11 of the 14 patients in whom the dose had been higher. None of the patients sustained obvious damage to the optic nerve.

ZUSAMMENFASSUNG

Dreissig Patienten, die 7 bis 30 Jahre zuvor mit Tiefenbestrahlung wegen eines Tumors des Nasenrachenraumes behandelt worden waren, wurden ophthalmologisch auf Strahlenschädigung des Auges untersucht. Trübungen der Linse wurden in 25 Patienten gefunden, in 19 zeigten sich die typischen Formen eines Strahlenkataraktes. Retinochorioidale Schädigungen zeigten sich in einem von 6 Fällen, in denen die absorbierte Strahlendosis weniger als 2500 rad in 3 bis 5 Wochen gewesen war und in 11 von 14 Patienten, in denen die Dosis höher gewesen war. In keinem Falle konnte eine Schädigung des Nervus opticus mit Sicherheit nachgewiesen werden.

RÉSUMÉ

Les auteurs ont fait un examen ophtalmologique pour rechercher des lésions tardives à 30 malades qui avaient été traités par radiothérapie de 7 à 30 ans auparavant pour des tumeurs naso-pharyngiennes. Vingt-cinq de ces malades avaient des opacités dans le cristallin, chez 19 ces opacités avaient des caractéristiques semblables à celles de la cataracte due aux radiations. Il y avait des lésions choroïdo-rétiniennes évidentes chez un des 6 patients chez lesquels la dose absorbée estimée avait été inférieure à 2 500 rad en 3 à 5 semaines et chez 11 des 14 malades chez lesquels la dose avait été supérieure. Aucun des malades n'avait subi de lésion certaine du nerf optique.

REFERENCES

1. AXELSSON, U. and HOLMBERG, Å.: The frequency of cataract after miotic therapy. Acta ophthal. 44 (1966), 421.
2. BENNER, S., RAGNHULT, I. and GEBERT, G.: Miniature ionization chambers for measurements in body cavities. Phys. in Med. Biol. 4 (1959), 26.
3. BIEGEL, A. C.: Experimental ocular effects of high voltage radiation from the betatron. Arch. Ophthal. 54 (1955), 392.



Fig 1 Specimen roentgenogram of pectoral muscles with three black spots produced by ^{198}Au-emission in three histologically proved lymph nodes (dorsal surface of specimen facing the film)



Fig 2 Specimen roentgenogram of the breast and the pectoral muscles A black spot produced by ^{198}Au-emission in one histologically proved lymph node on the dorsal surface of the pectoral muscle facing the film this node contained marginal metastasis

(1963) and ROSENQVIST (1966) who in Sweden recommended the modified radical mastectomies declared that the interpectoral nodes seem to be of no importance as a metastatic station in carcinoma of the breast

The lymphatics in the retromammary space — deep fascial plane (GRAY) — have been studied by injection of dyes and radioactive tracer into the mammary gland by TURNER WARWICK (1959) This author concluded that the minute lymphatics on this fascial plane are of no importance in the pathways of lymphatic drainage of the breast and play no part in the early spread of mammary carcinoma A few quite large lymphatics leave the posterior surface of the breast accompanying the larger perforating blood vessels They pass across the retromammary space entering the pectoralis major or intercostal space with no suggestion of a plexiform arrangement These penetrating lymphatics which pass vertically are in the opinion of TURNER WARWICK of considerable importance

FROM THE DEPARTMENTS OF SURGERY II (DIRECTOR PROF R ROMANUS), PATHOLOGY II (DIRECTOR PROF S LANSTRÖM), RADIOTHERAPY (DIRECTOR PROF M STRANDQVIST), ROENTGENDIAGNOSTIC DEPARTMENT II (DIRECTOR PROF I WICKBOM), AND DEPARTMENT OF RADIOPHYSICS (DIRECTOR ASSOC PROF H SKÖLDBORN), GOTHENBURG, SWEDEN

LYMPHATIC SPREAD OF MAMMARY CARCINOMA

Role of non-interpectoral lymph nodes on dorsal surface of pectoralis major muscle and of interpectoral nodes

by

A HULTBORN, L HULTÉN, B ROOS, M ROSENCRANTZ, B ROSENGREN and CH AHREN

Removal of both pectoral muscles has formed a part of the standard technique in radical mastectomy for nearly three quarters of a century. The interpectoral nodes are extirpated in this way and the lymphatic plexus in the retromammary space between the mammary gland and the anterior fascia on the pectoralis major muscle, the so-called deep fascial plane, is also removed. This has been considered necessary for the local eradication of the disease. It has also been stated that removal of the pectoral muscles is necessary for an adequate dissection of the axilla.

The efficiency of axillary dissection with preservation of one or both pectoral muscles will not be discussed in this paper. Supporters of these modified forms of radical mastectomy have paid little attention to the fact that the interpectoral nodes are difficult to remove in these types of operation. ROSENQVIST & ERWALD

Submitted for publication 9 January 1970



Fig 1 Specimen roentgenogram of pectoral muscles with three black spots produced by ^{198}Au emission in three histologically proved lymph nodes (dorsal surface of specimen facing the film)



Fig 2 Specimen roentgenogram of the breast and the pectoral muscles A black spot produced by ^{198}Au emission in one histologically proved lymph node on the dorsal surface of the pectoral muscle facing the film this node contained marginal metastasis

(1963) and ROSENQVIST (1966) who in Sweden recommended the modified radical mastectomies declared that the interpectoral nodes seem to be of no importance as a metastatic station in carcinoma of the breast

The lymphatics in the retromammary space — deep fascial plane (GRAY) — have been studied by injection of dyes and radioactive tracer into the mammary gland by TURNER WARWICK (1959) This author concluded that the minute lymphatics on this fascial plane are of no importance in the pathways of lymphatic drainage of the breast and play no part in the early spread of mammary carcinoma A few quite large lymphatics leave the posterior surface of the breast accompanying the larger perforating blood vessels They pass across the retromammary space entering the pectoralis major or intercostal space with no suggestion of a plexiform arrangement These penetrating lymphatics which pass vertically are in the opinion of TURNER WARWICK of considerable importance

The aim of the present investigation was to determine whether the lymph from

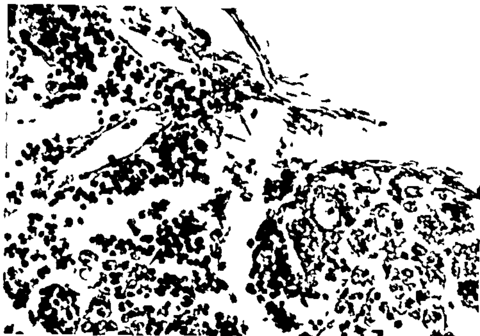


Fig 3 Histologic section of the lymph node referred to in fig 2 with marginal metastasis Aggregates of ^{198}Au are indicated by arrows van Giesen ×210

the mammary gland drains to regional lymph nodes outside the axillary, internal mammary and supraclavicular nodes and furthermore if such nodes are left behind in modified radical mastectomy with preservation of the pectoral muscles

Eight patients with carcinoma of the breast were subjected to radical mastectomy including removal of the pectoral muscles following injection of ^{198}Au into the parenchyma of the breast and intralymphatic Lipiodol injected into the dorsum of the hand

The examination procedures of the specimens and analysis of the lymph nodes have been described in detail earlier (HULTBORN et coll 1970) The postoperative investigations of the specimen included roentgen exmination, quantitative measurements of radioactivity autoradiography and histologic examination

Results and Discussion

In four of the eight operated patients, seven lymph nodes were demonstrated on the dorsal aspect of the pectoralis major muscle, outside the pectoralis minor In a fifth patient, one lymph node lay in the plane between the pectoral muscles, i e interpectorally Four of the seven nodes situated dorsal to the pectoralis major had a Lipiodol content (though this could be demonstrated only at microscopy in two lymph nodes), whereas six of the seven nodes contained radioactivity

Lymph nodes with high radioactivity (blackening the roentgen film) were located on the dorsal aspect of the pectoralis major muscle (Figs 1 and 2) Metastasis was also present in one of these node. (Fig 3) Neither radioactivity nor Lipiodol was observed in the lymph node demonstrated interpectorally

It was found in the present investigation that in five of the eight patients lymph nodes were situated on the dorsal surface of the pectoralis major muscle and in four of them outside the pectoralis minor In three patients the lymph nodes contained radioactivity

It may be argued that the distribution of radioactive material does not necessarily reflect pathways for metastatic spread Notably however one of these patients also had metastasis in one of the nodes situated on the *dorsal aspect of* the pectoralis major and outside the pectoralis minor This patient had a tumour measuring 2 cm × 3 cm retraction of the nipple and four axillary lymph node metastases with perinodular infiltration

The conclusion must thus be drawn that mammary carcinoma may also spread through the deep fascial plane and the pectoralis major muscle to lymph nodes on the dorsal surface of the latter This means that from a surgical point of view saving *the pectoral muscles* must be hazardous in the treatment of mammary carcinoma This attitude naturally presupposes that regional lymphadenectomy *contributes* to the eradication of the disease

SUMMARY

Eight patients with carcinoma *of the breast* were investigated by injection of ^{198}Au into the mammary parenchyma and *lymphography via the* lymph vessels on the dorsum of the hand The spread of carcinoma of the breast through the deep fascial plane and pectoralis major muscle to *lymph nodes* on *the* dorsal surface of the latter is described These regional nodes must also be *of in*terest in the choice of the type of radical mastectomy

ZUSAMMENFASSUNG

Acht Patienten mit Brustkarzinom wurden *mittels* ^{198}*Au Injektion* in das Brustparenchym und mit Lymphographie der Lymphgefasse am Dorsum der Hand untersucht Die Ausbreitung vom Brustkarzinom durch die *tiefe Fascie* und den Musculus pectoralis major zu den Lymphknoten dessen dor*salen Oberflache* wird beschrieben Diese regionaren Knoten mussen auch die Wahl von radikaler *Brustamputation* beeinflussen

RÉSUMÉ

Huit malades atteints de cancer du sein ont ete examinees par injection de ^{198}Au *dans* le parenchyme mammaire et *par lymph*ographie des vaisseaux lymphatiques du dos de la main Les auteurs decrivent l extension du *cancer* du sein a travers le fascia profond et à travers le muscle grand pectoral jusqu aux *ganglions* lymphatiques situes a la face postérieure de ce muscle Ces ganglions regionaux *doivent* presenter un interet dans le choix du type de mastectomie radicale

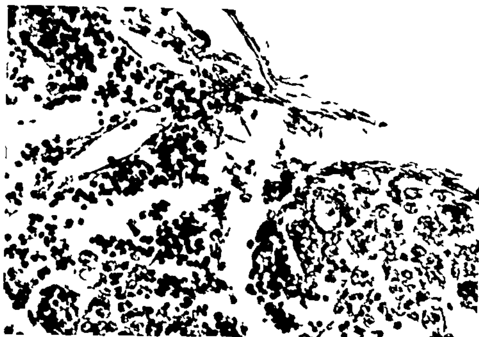


Fig 3 Histologic section of the lymph node referred to in fig 2 with marginal metastasis Aggregates of ^{198}Au are indicated by arrows van Giesen ×210

the mammary gland drains to regional lymph nodes outside the axillary, internal mammary and supraclavicular nodes and furthermore if such nodes are left behind in modified radical mastectomy with preservation of the pectoral muscles

Eight patients with carcinoma of the breast were subjected to radical mastectomy including removal of the pectoral muscles following injection of ^{198}Au into the parenchyma of the breast and intralymphatic Lipiodol injected into the dorsum of the hand

The examination procedures of the specimens and analysis of the lymph nodes have been described in detail earlier (HULTBORN et coll 1970) The postoperative investigations of the specimen included roentgen examination, quantitative measurements of radioactivity autoradiography and histologic examination

Results and Discussion

In four of the eight operated patients, seven lymph nodes were demonstrated on the dorsal aspect of the pectoralis major muscle outside the pectoralis minor In a fifth patient, one lymph node lay in the plane between the pectoral muscles, i e interpectorally Four of the seven nodes situated dorsal to the pectoralis major had a Lipiodol content (though this could be demonstrated only at microscopy in two lymph nodes), whereas six of the seven nodes contained radioactivity

FROM THE DEPARTMENTS OF PATHOLOGY II AND RADIOBIOLOGY, THE GUSTAF WERNER INSTITUTE, THE UNIVERSITY OF UPPSALA SWEDEN

EFFECTS OF THERAPEUTIC PROTON DOSES ON HEALTHY ORGANS IN THE NECK, CHEST AND UPPER ABDOMEN OF THE RABBIT

by

M Danielsson B Engfeldt B Larsson Chr Naeslund and J Naeslund

Experimental and clinical investigations on the effect of therapeutic proton doses have been mainly concerned with malignant growth and healthy tissues in the pelvis minor (Naeslund et coll 1959 Falkmer et coll 1962, Fors et coll 1964 Danielsson et coll 1968) and in the head (Graffman, Hugosson et coll 1967 Graffman Jung et coll 1967) The single dose used in the investigation now reported, 3 000 rad or its fractionated equivalent seems to represent an upper limit for doses applicable in tumour therapy At this dose level, the proton radiation seems to affect the primary tumour and its metastases in a way similar to other sparsely ionizing radiation in therapeutic use The situation in the healthy tissues is less clear in the above mentioned reports but the protons seem generally to have caused little damage This agrees with the results of early experiments on rabbit ears (Naeslund et coll 1958) and in particular recent investigations by Stenson (1969) who found that the ratio between roentgen and proton doses creating histologically equivalent damage in the rat rectum was in the range 0 6—0 7

This work was supported by the Swedish Cancer Society Submitted for publication 20 April 1970

REFERENCES

Gray's anatomy, pp 924 1550 Longmans London 1962

HULTBORN A, HULTÉN L, ROOS B et coll Evaluation of regional lymph drainage from mammary gland and hand to axillary nodes Acta radiol Ther Phys Biol 9 (1970) 489

— — — — Topography of lymph drainage from mammary gland and hand to axillary lymph nodes Acta radiol Ther Phys Biol 10 (1971), 65

ROSENQVIST H Kirurgisk behandling av brostcancer (In Swedish) Lakartidningen 63 *(1966), 1023*

— och ERWALD R Brostcanceroperationen (In Swedish) Opusc med 2 (1963) 36

TURNER WARWICK R T The lymphatics of the breast Brit J Surg 46 (1959) 574

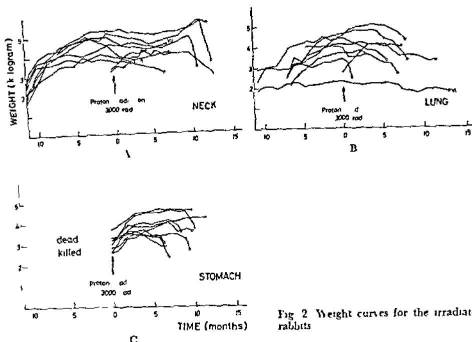


Fig 2 Weight curves for the irradiated rabbits

during which the animals were kept at the animal cages before irradiation is seen from the weight diagrams in Fig 2

Trachea and oesophagus Rabbits A I to A IX were used for this experiment The rabbits were anaesthetized with 20 % nembutal solution (Abbot 1 ml/kg body weight) injected into an aural vein through a polythene cateter (size 50) The catheter was kept in situ throughout the treatment so that when necessary additional injection could easily be given The rabbit was strapped in the supine position to a Lucite stand which was then placed with the frontal plane of the rabbit at right angles to the axis of the beam and with the front of the animal facing the incoming beam The stand with the rabbit lay with its longitudinal axis horizontal so that the radiation field of 4 cm × 6 cm covered the neck its longest side being perpendicular to the longitudinal axis of the animal A ridge filter (LARSSON 1961) and absorbers were placed in the beam so that a 5 cm plateau of the depth dose curve contained the thickness of the neck The dose rate in the plateau varied between 50 and 100 rad/minute

The rabbits were weighed once weekly and their general condition was observed White blood cell and haemoglobin determinations were made before and after the treatment

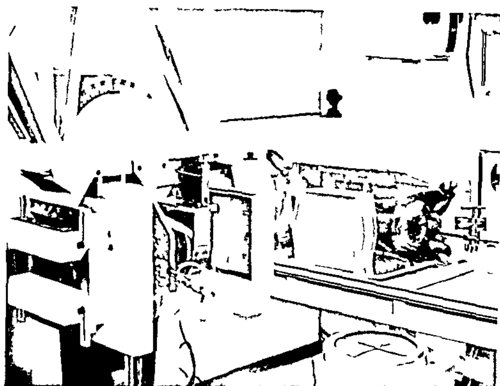


Fig 1 Set up for irradiation of the stomach. The collimated 185 MeV proton beam passes through a 3 cm × 4 cm aperture, a parallel plate ionization chamber, a ridge filter and a Lucite absorber. The plateau of the depth dose curve contained the thickness of the animal.

The present report concerns screening for possible untoward effects of proton radiation on healthy tissues in organs not previously investigated. To permit comparison with previous work a single dose of 3 000 rad was chosen. It was given to the neck, chest, or upper abdomen, and particular consideration was given to the effects on the oesophagus, trachea, lungs and stomach. In a following paper the problem of fractionation, in the case of lung irradiation, will be considered separately (ENGFELDT et coll.).

Material and Methods

Irradiation was performed with the external 185 MeV proton beam from the 230 cm synchrocyclotron under the general conditions described by LARSSON (1961). The absorbed dose was in all cases 3 000 rad and single. It was determined with parallel plate ionization chambers at an estimated uncertainty of less than ± 5 %. The fluency homogeneity was in the range ± 5 %.

Three separate experiments were performed, each on nine rabbits. The period

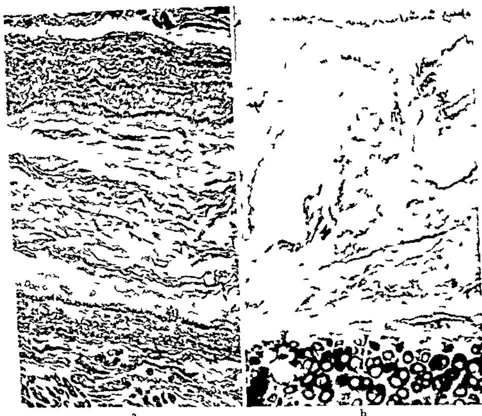


Fig 3 Sections from the neck organs in rabbit A I about one year after irradiation a) Oesophagus b) Trachea

neck where the proton beam had emerged almost complete epilation and dermatitis were seen in all cases and in seven animals ulceration that did not heal for several months

One rabbit A III displayed disturbed balance and deflection of the head to one side a few months after irradiation and this condition persisted for some time This rabbit had severe curf on both ears

Blood tests before proton irradiation gave the following values haemoglobin 62—70 % mean value 67 % white blood cells 3 900—7 660/mm³, mean value 6 200 mm³ with 28 % mononuclear cells Two months after irradiation somewhat higher values were obtained haemoglobin 60—74 % mean value 72 % white blood cells 7 900—13 700/mm³ mean value 8 700/mm³ with 32 % mononuclear cells

The period of observation and the time of autopsy are seen in Fig 2 Autopsy

Lungs In rabbits B I to B IX the entire right lung was irradiated The position of the lung was determined by a roentgen technique ensuring that the radiation field, which measured 4 cm × 6 cm, covered the right half of the chest The radiation technique was in other respects the same as described above

In the course of the investigation the animals were kept under observation and weighed approximately once weekly White blood cell and haemoglobin determinations were made both before and after irradiation

Stomach Rabbits C I to C-IX were all irradiated by a field of radiation, 3 cm × 4 cm, so arranged that the center of the beam met the animal 0 5 cm to the left of the midline and 1 5 cm below the base of the lung (Fig 1) For this group Lucite absorbers and the ridge filter described by KARLSSON (1964) were used, so arranged that the thickness of the animal was contained in the plateau region The dose rate in the plateau varied between 50 and 100 rad/minute A photographic film irradiated in front of the Lucite plates on the side facing the incoming beam showed a pattern of regular stripes after development, while a film between the absorber and the rabbit was homogeneously darkened The estimation was made that the relative dose variation in the animal due to the structure of the filter was in the range ± 5 % These rabbits were usually not anaesthetized but they nevertheless lay still during irradiation, as was ascertained by television

The general condition of the rabbits was observed and recorded in the course of the investigation, and their weights were registered once weekly

Results

The experimental observations will now be reported separately for the three experiments

Trachea and oesophagus Seven of these rabbits (A-I to A VII which were in the stable one year before irradiation had normal weight increase during this time After irradiation, the increase was only negligible, or the weight remained unchanged, except in three cases (A III, A IV and A V) in which the weight decreased considerably just before death (in bilateral bronchopneumonia) The general condition of the animals is thus well reflected in the weight diagram (Fig 2)

Animals A-VIII and A IX on the other hand, which had been bought immediately before irradiation, increased distinctly in weight during the first few months after treatment Their weights then remained more or less unchanged

More or less severe epilation was seen on the front of the neck 1 to 2 months after irradiation, and in two rabbits slight dermatitis On the dorsal side of the

lung where pleuritis and leucocytic exudate in the bronchi were also seen In this rabbit nothing abnormal apart from oedema was seen in the left lung The remaining rabbits had pneumonic changes in both lungs, fibrosis and degeneration, and fusion of the alveoli The changes were in the main similar in both lungs but in two rabbits (B VI and B VIII) the inflammatory infiltration was more marked in the right lung Profuse inflammatory exudate was also seen in the bronchi In B III pleuritic changes were present in both lungs although they were more extensive on the right side

Stomach The general condition showed good agreement with the weight curves These rabbits had a fairly constant weight increase during the first two months after irradiation (Fig 2) and with the exception of C II which had an upper respiratory infection during the third month, the weight continued to increase slightly even later During the period immediately before death the weight suddenly decreased except in C VI and C-VII who were killed ten months after irradiation The animals had a good general condition during the main observation period and deteriorated only immediately before death Two rabbits (C-III and C IX) showed signs of weakness of the hind limbs during their last few weeks

During the second month all animals exhibited epilation on the irradiated skin area It was less severe ventrally than on the back where the proton beam had emerged There the epilation was generally complete and in C I C V and C VII ulceration had occurred The period of observation and the time of autopsy are seen in Fig 2 All rabbits were still alive six months after irradiation During the seventh month C IX died and C II and C III were killed The remaining rabbits lived until the ninth to eleventh months when two died and four were killed

In C-II with an upper respiratory infection autopsy revealed right sided pleural empyema and an abscess in the right lung In the left lung moderately extensive infiltration and slight oedema were observed In the liver marked degeneration of the parenchyma was seen, with extreme stasis In histologic sections from the stomach the mucosa was seen to be of normal height and there were no definite changes In C III and C-IX who had had paralysis of the hind limbs and who were killed or died after seven months, autopsy revealed oedema in the lung and fusion of the alveoli and inflammatory exudate in the bronchi The gastric mucosa was of normal height in both cases, with no definite changes In C V who died during the tenth month autopsy revealed an abscess in the thoracic cavity and microscopic examination of the lungs showed oedema and in places inflammatory infiltration In C VI also who was killed after ten months extensive broncho-pneumonic lesions were seen which in some places

revealed bilateral bronchopneumonic infiltration in A VIII (2 1/2 months) and in A-VII (7 months) and also in four rabbits, A I, A-III, A-IV and A V, who died or were killed approximately one year after irradiation No obvious changes were observed on macroscopic examination of the neck organs at autopsy

Microscopic examination of the oesophagus showed nothing pathologic in any of the animals (Fig 3a) In microscopic preparations from the trachea, oedema and dilated blood filled vessels and also *round cell infiltration in the mucosa* were seen in A-I to A VII (Fig 3b) In A-II, parts of the mucosa were also eroded, and towards the lumen some detritus masses were seen In A-V, even the regions surrounding the trachea displayed oedema and lymphocytic infiltration In A IX, who was killed after five months, the trachea showed further changes in the form of poor basophilia, with a suggestion of necrosis of the cartilage, and also desquamated mucosal epithelium, which was partly eroded In A VIII, who died in bronchopneumonia 2 1/2 months after irradiation, the changes in the tracheal mucosa were even more accentuated, with haemorrhages and necrosis in superficial regions *and also profuse inflammatory cell infiltration In addition, the* cartilage had in parts lost its stainability and showed signs of degeneration in small areas

Lungs One rabbit died 26 days before irradiation and autopsy revealed bilateral bronchopneumonia This rabbit was replaced by another (B IX) The general condition of the irradiated rabbits is reflected in the weight diagram (Fig 2) Rabbits B I to B VIII who had been observed for a long period before irradiation mostly had little weight increase or reduction during a long period after irradiation *The general condition deteriorated shortly before death*, when also a dramatic weight decrease was seen The weight curve for rabbit B IX was different, the weight of this animal increased by 50 % during the three months immediately following treatment

In all animals, epilation and slight dermatitis were observed on the right ventral side of the chest between one and two months after the irradiation No ulceration occurred and the skin conditions regressed gradually On the right side of the dorsal region considerably more severe changes, with complete epilation and dermatitis and, in six cases, ulceration, were observed

The *period of observation* and the time of autopsy are given in Fig 2 At autopsy, oedema and emphysema in both lungs were present in B I and B IV, who died 7 1/2 months after irradiation In addition, there was regressively changed cartilage in the right lung of B I No inflammatory infiltration was observed in these rabbits The remaining rabbits, in addition to signs of pulmonary oedema and emphysema had bronchopneumonic infiltration In B IX dead seven months after irradiation, such infiltration occurred only in the right

observed at the time of examination The gastric mucosa was of normal height and of normal architectonics

It may be concluded that no pathologic changes in the oesophagus, trachea lung or stomach could be safely ascribed to the radiation treatment and no constant signs of a decreased general condition of the rabbit were noted throughout the main observation period The findings are in conformity with previous observations after abdominal irradiation (NAESLUND et coll 1959 DANIELSSON et coll 1968)

SUMMARY

Proton irradiation of the neck region the lung or stomach in the rabbit with 3 000 rad in a single dose did not cause any obvious pathologic changes

ZUSAMMENFASSUNG

Protonen Bestrahlung der Nackenregion der Lunge oder des Magens des Kaninchens mit 3 000 rad in einer Dosis fuhrte zu keinen augenscheinlichen pathologischen Veranderungen

RÉSUMÉ

L irradiation par des protons a une dose unique de 3 000 rad sur la *region cervicale* le poumon ou l estomac du lapin n entraine aucune modification pathologique evidente

REFERENCES

DANIELSSON M ENGFELDT B FORS B et coll Effect of high *energy protons on* Vx2 carcinoma implanted in the lower abdominal wall of the rabbits Acta obstet gynec scand 47 (1968) 373

ENGFELDT B LARSSON B NAESLUND C *et coll* Effect of single dose or fractionated proton irradiation on pulmonary tissue and Vx2 carcinoma in lung of rabbit To be published in Acta radiol Ther Phys *Biol*

FALKMER S FORS B LARSSON B et coll Pilot study on proton irradiation of human carcinoma Acta radiol 58 (1962) 33

FORS B LARSSON B LINDELL A et coll Effect of high energy protons on human genital carcinoma Acta radiol Ther Phys *Biol 2 (1964) 384*

GRAFFMAN S HUGOSSON R JUNG B and NOHRMAN B A High energy protons in the postoperative treatment of glioblastoma multiforme Proc XIth *Internat* Congress Radiology Rome September 1965 Excerpta med Intern Congress Series No 105 (1967) p 1 050

— JUNG B NOHRMAN B A and BERGSTROM R Supplementary treatment of nasopharyngeal tumours with high energy protons Acta radiol Ther Phys Biol 6 (1967) *361*

KARLSSON B Über *die* Bestimmung und Erziehung einiger für die Tiefentherapie mit Protonen gunstigen Dosisverteilungen *Strahlentherapie 124 (1964)* 481

LARSSON B Pre therapeutic *physical* experiments with high energy protons Brit J Radiol 34 (1961) 143

were undergoing organization Sections from these two rabbits showed a gastric mucosa of normal architectonics and no pathologic changes In C I, C IV, C VII and C VIII essentially the same autopsy findings were made There were oedema and emphysema in the lungs and, in places, fibrosis and hyaline areas Sections from these animals showed microscopically a gastric mucosa of normal architectonics and height

Discussion

The results indicate that a single proton dose of 3 000 rad did not cause severe damage of the inner organs studied, i e the trachea, oesophagus, lungs and stomach Most animals were in a good condition throughout the period of observation and their weights either increased or remained at a high level Unfortunately, a relatively high incidence of bronchopneumonia was observed in all three series It appears, however, that the site of these changes does not necessarily conform with the irradiated lung region Thus, at autopsy, six animals were found to have bilateral pneumonia after irradiation of the neck region or the stomach However, one rabbit in the lung group died in bilateral bronchopneumonia some time before irradiation

After proton irradiation of the neck, no or only moderate pathologic changes were seen in the irradiated region Macro and microscopic examination of the oesophagus disclosed nothing abnormal in any rabbit In the trachea, although no macroscopic changes were found, the microscopic examination revealed oedema and dilated vessels and sometimes round cell infiltrations in the mucosa There was also in one rabbit a desquamated and partly eroded mucosal epithelium, poor basophilia and a suggestion of necrosis This damage was not directly attributed to the effect of irradiation

In most lung irradiated rabbits more or less marked bronchopneumonic infiltration and inflammatory exudate in the bronchi were observed Approximately similar changes were present in both lungs in all these rabbits, except one In this latter rabbit who died seven months after irradiation, autopsy revealed, in the right lung bronchopneumonic infiltration, oedema, pleuritis and leucocytic exudate in the bronchi, while oedema was present only in the left lung This localization of the inflammatory changes to the right lung may conceivably have been connected with the proton irradiation seven months previously Autopsy in two rabbits showed only oedema and emphysema In one of them, regressive cartilaginous changes were seen in some of the bronchi of the right lung This seemed to be the only marked alteration in the lung caused by irradiation

After irradiation of the stomach, no macroscopic or microscopic changes were

FROM THE DEPARTMENT OF GYNECOLOGY (DIRECTOR PROF H L KOTTMEIER), RADIUMHEMMET AND THE DEPARTMENT OF CLINICAL RADIOPHYSICS (DIRECTOR PROF R WALSTAM) THE NATIONAL INSTITUTE OF RADIATION PROTECTION STOCKHOLM SWEDEN

SHIELDED INTRA UTERINE APPLICATOR FOR A REMOTE AFTERLOADING TECHNIQUE IN THE TREATMENT OF CARCINOMA OF THE UTERINE CERVIX

by

ANDERS BACKSTROM and INGEMAR JOELSSON

Afterloading techniques (WALSTAM 1965) coupled with the availability of medium or low energy gamma radiation sources of high specific activity have stimulated interest in refinements in the utilization of shields incorporated in the applicator The aim of cour e is the protection of intrapelvic visceral organs A series of such intracavitary applicators has been constructed at Radiumhemmet and one of the shielded vaginal applicators has previously been de cribed (JOELSSON & BACKSTROM 1970) As the next step an intra uterine applicator with an anterior shield has been developed

Design of the intra uterine applicator It was decided to maintain an outer diameter of 9 mm for the intra uterine applicator The wall thickness was reduced to 0 5 mm a minimal figure if structural strength was not to be com

This work was supported by grants from the *Cancer Society of Stockholm* and the King Gustaf V Jubilee Fund Submitted for publication 30 June 1970

NAESLUND J, STÉNSON S and LARSSON B Results of proton irradiation of Vx2 carcinoma in the uterus of rabbits Acta obstet gynec scand 38 (1959) 563
— — FALKMER S et coll Concerning the effects of proton radiation on Vx2 carcinoma and normal skin in rabbit ears Acta Soc Med upsalien 63 (1958) 155
STENSON S Effect of proton and roentgen radiation on the rectum of the rat Acta radiol Ther Phys Biol 8 (1969), 263

Table

Dose rates in rad h at 10 and 25 mm distances from the external surface of the applicator in anterior posterior and lateral directions Figures in parenthesis represent dose rates as a percentage of the value at 10 mm from the applicator in the posterior direction

Directions	10 mm from the external surface		25 mm from the external surface	
Anterior	336	(55)	146	(24)
Posterior	606	(100)	236	(39)
Lateral	478	(78)	214	(35)

layer of decreasing thickness in the range of 2 8—0 mm in lateral directions A cross-section and a longitudinal section of the applicator are presented in Fig 1

Methods of dose measurements and isodose registration Dose measurements in the surrounding volume of the applicator were performed with dosemeters of lithium borate (Li B₄O Mn) in teflon at 10 and 25 mm distances from the outer surface of the applicator in anterior posterior and lateral positions in a plane through the center of symmetry of the train of radiation sources The consistent and reproducible relationship between the sound and the dosemeters was assured by means of a specially shaped perspex fixture in the water phantom The standard deviation of the results of the thermoluminescent measurements as a percentage of the mean was 3 1 in the application described

Isodose curves about the intra uterine applicator in two perpendicular planes were determined by means of an automatic isodose recorder (LARSSON et coll 1963) The radiation energy dependence of the antracene crystal of the recorder was estimated to be within ± 5 % for actual energy range The error in correctly plotting the locus of the isodose curves relative to the center of the applicator was estimated to ± 1 mm for the distances of interest The applicator was loaded with 620 mCi [13] Cs divided into six sources

Results

The mean dose rate was 606 rad/h at 10 mm distance from the posterior surface of the applicator a value used for normalization purpose and set at 100 % The dose rate was observed to be 55 % at an identical distance from the anterior surface of the applicator and at the same distance from the outer surface of the applicator in lateral directions the rate was 78 %

The dose rate in a posterior direction was 39 % at 25 mm distance from the

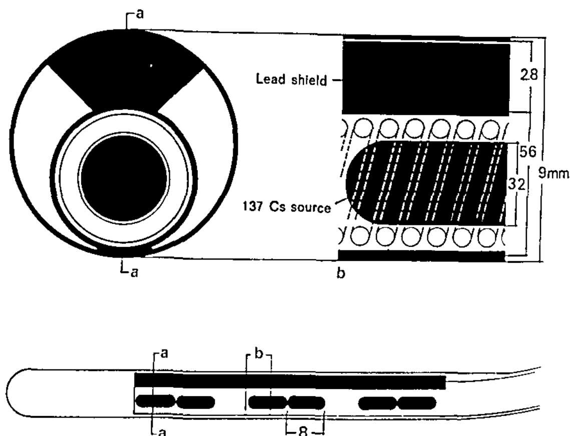


Fig. 1. The shielded applicator in transverse and longitudinal sections. Dummies of brass lie in the empty spaces in the source train.

promised. With the present dimensions of the train of radiation sources, 2.8 mm represented the maximal thickness of the shielding that could be incorporated in the anterior surface of the applicator. Lead was utilized for the shield in the construction of the experimental applicator model. It is appreciated, however, that the figure of the first HVL is high and compares unfavorably with that of platinum and gold. The calculated narrow beam attenuation with a 2.8 mm layer of lead, 18 carat gold, pure gold and platinum increases from 30 to 37, 42 and 46 % respectively. Uranium or tungsten, with their more favorable characteristics for the first HVL, was not incorporated because of mechanical considerations in the first experimental fabrication (GRODSTEIN 1957, THORAEUS 1965).

The sector occupied by the full thickness of lead in the intra uterine applicator is at an angle of 50° in relation to the center of the radiation sources, displaced in a posterior direction. A sector corresponding to an angle of 10° holds a lead

bination with the ring shaped vaginal applicator with the gold screens referred to above It is to be noted that the maximal shielding effect of the vaginal and of the intra uterine applicators do not anatomically apply to the same tissue volume Thus the maximal dose reduction in an anterior direction about the et of combined applicators does not correspond to the sum of the maximal shielding effect of the intra uterine and vaginal applicators separately

SUMMARY

The construction and physical characteristics of an intra uterine applicator for a remote afterloading technique are described Shielding material was placed in an anterior direction and the channel for the radiation sources displaced to lie along the posterior wall A considerable reduction in the dose rate in the direction of the urinary bladder was obtained as a consequence of the applicator design

ZUSAMMENFASSUNG

Die Konstruktion und die physikalischen Eigenschaften eines intrauterinen Applikators für eine Fern Nachlade technik werden beschrieben Schützendes Material wurde in der vorderen Richtung angebracht und der Kanal für die Strahlenquelle entlang *der hinteren Begrenzung* verlegt Es wurde als Folge dieser Konstruktion des Applikators eine bedeutende *Herabsetzung der Dosis Rate* in Richtung auf die Harnblase erreicht

RÉSUMÉ

Les auteurs décrivent la construction et les caractéristiques physiques d un applicateur intra utérin *pour une technique* de chargement retardé à distance Le matériau de protection est placé en avant et le tube pour *les sources de radiation* est déplacé de façon à être situé le long de la paroi postérieure La configuration de cet applicateur a entraîné une réduction considérable *du débit* de dose en direction de la vessie

REFERENCES

GRODSTEIN G W X ray attenuation coefficients from 10 keV to 100 MeV National Bureau of Standards Circular 583 Washington 1957

JOELSSON I and BÄCKSTRÖM A *Applicators for remote afterloading technique for optimum pelvic dose distribution in carcinoma of the uterine cervix* Acta radiol Ther Phys Biol 9 (1970) 233

KOTTMEIER H L Personal communication (1969)

LARSSON L LIDÉN K and STARFELT N Automatic isodose recorder *Acta radiol Ther Phys Biol* 1 (1963) 99

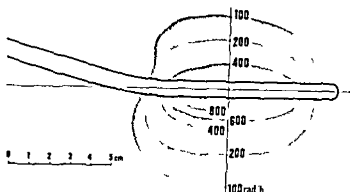


Fig 2 Dose distribution in the anatomic sagittal plane through the center of the intra uterine applicator

outer surface of the sound and in an anterior direction amounted to 24 %. The rate was 35 % in lateral directions. *These observations are tabulated in the Table*

The isodose rate curves in the principal longitudinal plane through the applicator (corresponding to the anatomic sagittal plane) are presented graphically in Fig 2. The spatial distribution of these dose rates in the plane perpendicular to the previous one (corresponding to the anatomic frontal oblique plane) through *the geometric center of the intra uterine applicator is given below*

Dose rates in rad/h	800	600	400	200	100
Distances in mm from external surface of applicator in lateral directions	5	8	13	26	36

Discussion

The intracavitary applicators for remote afterloading at Radiumhemmet have hitherto been held in position by means of a steel bar and corset system. As has been repeatedly observed, even heavy applicators can be fully supported, and their weight has not been a limiting factor in the construction. This is in contrast to the shielded applicators described by NEARY (1943, 1947) and NOLAN (1962), the use of which *led to complications*, necrosis for instance of the vaginal wall (KOTTMEIER 1969)

It proved advisable to take advantage of the combined effect of the shield and the displacement of the radiation sources in a posterior direction in the construction of the intra uterine applicator. As the total length of the train of sources is 58 mm the oblique incidence of the radiation from the sources in the end positions should cause a higher relative attenuation close to the applicator *wall than at a distance from it. This effect was confirmed during the measure*ments

The shielded intra uterine applicator was intended to be used also *in com*

FROM THE DEPARTMENT OF RADIOTHERAPY THE MOUNT SINAI SCHOOL OF MEDICINE
NEW YORK USA

AFTERLOADING HEYMAN APPLICATORS

by

N SIMON S M SILVERSTONE and L C ROACH

The packing method of treating cancer of the corpus of the uterus was introduced by HEYMAN of Radiumhemmet in 1930 Since then thousands of patients in numerous institutions throughout the world have been treated with this form of intracavitary radium therapy The packing of the uterus with Heyman applicators is a surgical procedure which requires experience and skill for the radiotherapist or surgeon must distend the uterine cavity with the applicators in order to get the most effective distribution of radium in the treatment of an endometrial carcinoma

Despite the universal use of the classical Heyman capsules there are obvious disadvantages to their use First Heyman capsules require surgical handling of hot radium capsules and this is associated with unnecessary radiation exposure to operators and to personnel in the operating rooms recovery room and roentgen diagnostic department Second the surgical procedure of packing the uterus is of limited accuracy when the radiotherapist or surgeon has to handle radioactive material he naturally hurries in order to minimize the radiation to himself and his associates

Radium is not suitable for afterloading the Heyman capsule because of the

Presented at the Meeting of the Groupe Europeen de Curietherapie Oxford 19 April 1970 Submitted for publication 6 April 1970

NEARY, G. J. The physical aspects of intracavitary radium treatment of carcinoma of the cervix uteri. Brit. J. Radiol. 16 (1943), 225, 263.

— Physical aspects of intracavitary radium treatment of carcinoma of the cervix uteri. Brit. J. Radiol. 20 (1947), 454.

NOLAN, J. F. Radiation treatment of carcinoma of the uterine cervix. *In* Treatment of cancer and allied diseases, vol. VI. Tumors of the female genitalia, p. 125. Edited by G. T. Pack and I. Ariel. Hoeber & Brothers, New York 1962.

THORAEUS, R. Attenuation of gamma radiation from ^{60}Co, ^{137}Cs, ^{192}Ir and ^{226}Ra in various materials used in radiotherapy. Acta radiol. Ther. Phys. Biol. 3 (1965), 81.

WALSTAM, R. Studies on therapeutic short distance and intracavitary gamma beam techniques. Acta radiol. (1965), Suppl. No. 236.

FROM THE DEPARTMENT OF RADIOTHERAPY THE MOUNT SINAI SCHOOL OF MEDICINE
NEW YORK USA

AFTERLOADING HEYMAN APPLICATORS

by

N SIMON S M SILVERSTONE and L C ROACH

The packing method of treating cancer of the corpus of the uterus was introduced by HEYMAN of Radiumhemmet in 1930 Since then thousands of patients in numerous institutions throughout the world have been treated with this form of intracavitary radium therapy The packing of the uterus with Heyman applicators is a surgical procedure which requires experience and skill for the radiotherapist or surgeon must distend the uterine cavity with the applicators in order to get the most effective distribution of radium in the treatment of an endometrial carcinoma

Despite the universal use of the classical Heyman capsules there are obvious disadvantages to their use First Heyman capsules require surgical handling of hot radium capsules and this is associated with unnecessary radiation exposure to operators and to personnel in the operating rooms recovery room and roentgen diagnostic department Second the surgical procedure of packing the uterus is of limited accuracy when the radiotherapist or surgeon has to handle radioactive material, he naturally hurries in order to minimize the radiation to himself and his associates

Radium is not suitable for afterloading the Heyman capsule because of the

Presented at the Meeting of the Groupe Europeen de Curietherapie Oxford 19 April 1970 Submitted for publication 6 April 1970

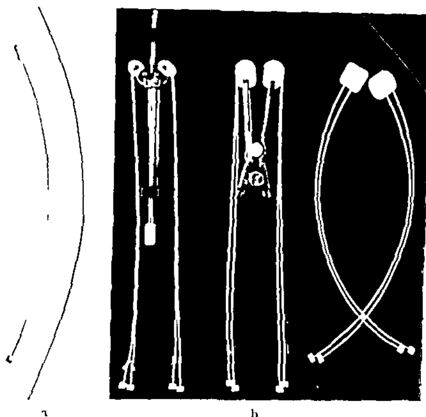


Fig 1 a) Heyman applicators Simon modification for afterloading The Simon afterloading modified applicator has a hollow plastic tube extending from the capsule instead of the braided wire in the usual Heyman applicator The afterloading plastic tube has a dummy wire insert for stiffness This is removed and replaced by a similar steel tube with radioactive cesium at its tip The dimensions of the afterloading capsule and the Heyman capsule are identical b) Afterloading tubes adapted for use with colpostats

thickness of the radium tube itself Very thin tubes are required Therefore, we must use high specific activity radionuclides as substitutes for the radium

Our modified Heyman applicators (Fig 1 a) are hollow plastic cylinders of the same size and shape as the original Heyman capsules, but instead of a braided wire we have a long thin hollow plastic tube leading from the capsule (Simon 1969) The lumen of the plastic tube is 1 mm in diameter and extends into the capsule A thin removable non radioactive steel wire in the plastic tubing and capsule provides structural rigidity for easy insertion of the capsule into the uterus The stiffness of the inert steel wire within the plastic tube makes it possible to apply enough force on the capsule to distend the uterine cavity In fact, the stiff plastic tube and its inactive wire provide a handle for the insertion of the capsule, making this insertion more easily controlled than with the usual Heyman appli

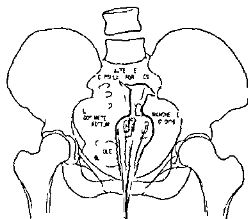
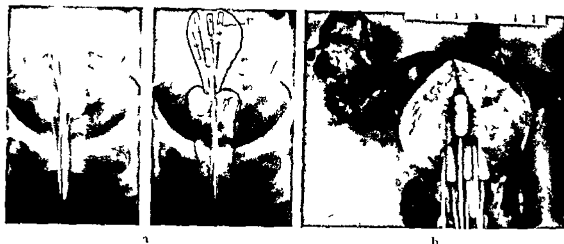


Fig 2 Diagram of three afterloading capsules in small uterine cavity After loading capsules have also been inserted into Manchester ovoids in the vaginal fornices

cator and its bulky inserting device After the uterine cavity has been appropriately packed with our modified Heyman applicators the inert wire is removed and replaced immediately by the dimensionally similar 18 gauge steel tubing containing the radioactive material in its tip The afterloading need not be done in the operating room it can be done at the patient s bedside or in the radiotherapy department

In the usual treatment of a patient with postmenopausal bleeding suggestive of carcinoma of the fundus of the uterus the diagnosis almost always must be established by dilatation and curettage under anesthesia Frozen section of the curettings is usually not sufficiently diagnostic and one must wait a day or two to get the pathology report If the report is positive for carcinoma the patient must again be anesthetized to pack the uterine cavity with classical Heyman applicators In contrast when afterloading applicators of the type presented in this paper are used they can be inserted at the time of the original dilatation and curettage for they are free of radioactive material and their insertion into the uterine cavity represents only a slight addition to the surgical procedure Further these capsules may be inserted into Manchester ovoids and adapted to other colpostats for irradiation of the vaginal vault (Fig 1 b)

Radioactive material The specific activity of radium is too low to provide the miniaturization required in afterloading the corpus of the uterus with multiple capsule Gamma emitters suitable for afterloading in our modified capsules are cesium 137 tantalum 182 cobalt 60 and iridium 192 We have elected to concentrate on the development of ^{137}Cs sources since this isotope has a suitably long half life 30 year and a lesser shielding requirement than radium Miniature encapsulation of cesium sources has been a problem but our devices are



a b

Fig 3 *Carcinoma in a slightly enlarged uterine cavity packed with seven afterloading capsules* a) Ap roentgenogram showing the capsules in uterus afterloading Manchester ovoids in vaginal fornices and Foley catheter in bladder b) *Specimen of uterus removed four days after* radiation with the afterloading capsules replaced

comprised of ^{137}Cs incorporated in porous glass (Vycor) in a cylinder 1 5 cm in length and of such narrow diameter that it fits in the lumen of 18 gauge needle tubing The porous glass absorbs a solution of ^{137}Cs into tiny chambers, and when the glass is heated, the cesium is permanently sealed in the chambers This glass cylinder containing the cesium is then encapsulated in the end of the steel tubing The activity of the cesium in our prototype devices is equivalent to 10 mg of radium (25 mCi of ^{137}Cs)

Thus far, we have inserted our modified Heyman afterloading applicators in ten patients, three at the time of dilatation and curettage for diagnosis All patients had postmenopausal bleeding which was highly suggestive of the diagnosis of adenocarcinoma of the fundus of the uterus Two cases were reported benign, and the afterloading capsules were therefore removed as soon as the pathology report was received The other 8 patients had radioactive cesium inserted It is of importance to indicate that the radiotherapist who inserted the radioactive cesium into the afterloading capsules received no more than 2 mR to a dosimeter in his breast pocket during the procedure This is in marked contrast to radiation exposure 10 to 100 times higher when Heyman capsules containing radium are packed into the uterine fundus

During the surgical procedure of inserting afterloading applicators, it is possible to pack carefully and deliberately It is possible even to teach an assistant how to do the procedure without the deterent of radiation exposure

Our modified Heyman applicator has been made to match the classical Heyman applicators, and we are using the Radiumhemmet technique in order to

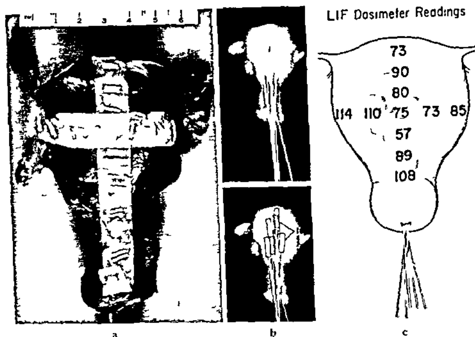


Fig 4 (Same case as fig 3) a) Uterus resutured capsules re loaded with ^{137}Cs LiF dosimeters affixed to serosal surface b) Roentgenogram of (a) showing distribution of intracavitary sources Compare with fig 3 a c) Dose distribution in rad per hour on surface of uterus Each of the seven capsules contains 25 mCi ^{13} Cs equivalent to 10 mg radium

minimize the variables in this clinical evaluation However hysterectomies have been performed in four of our patients a few days after the intracavitary radiation rather than the customary six weeks, the time interval which had been the basis of previous reports on the use of intracavitary radium Early hysterectomy affords us the opportunity to correlate the gross pathology with the distribution of our radioactive sources and also provides a specimen for direct measurement of the dose of radiation We use lithium fluoride dosimeters in the rectum vagina bladder and circumferentially around the excised uterus to obtain data which we will correlate with the classical measurements made at Radiumhemmet (HEYMAN et coll 1941 KARLSTEDT 1968)

Illustrations of the distribution of capsules in uteri with endometrial cavities of varying sizes are given in Figs 2 3 4 and 5

Discussion

It is a tribute to HEYMAN that his treatment methods evolved 40 years ago are still used with few modifications In carrying on the therapy of cancer of the

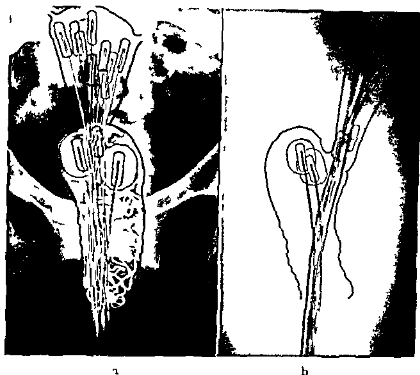


Fig 5 Carcinoma in a large uterine cavity packed with ten after loading capsules a) A p and b) lateral ronetgenograms showing intrauterine capsules and afterloaded Manchester ovoids in vaginal fornices

corpus of the uterus at Radiumhemmet, KOTTMEIER (1969) has individualized the indications for the use of intracavitary radium therapy In the United States, GUSBERG (1964, 1966) has been evolving criteria for staging and therapy stressing the prognostic significance of histologic differentiation and penetration of tumor into the myometrium KOTTMEIER and GUSBERG, although using slightly *different* staging methods, are in accord with the principle of treating the well differentiated early case of endometrial carcinoma by hysterectomy without intracavitary radiation KOTTMEIER would also follow operation by radiotherapy The question arises why this favorable category is not being treated with intracavitary radiation It is true that high 5 year cure rates have been attained in these cases by hysterectomy alone but it is also true that the exact state of histologic differentiation and penetration of tumor in such favorable cases is not always made at the time of dilatation and curettage There are fallibilities in histologic grading and difficulties in establishing the degree of penetration of tumor into muscle wall Thus it is reasonable to assume that some of these favorable early cases are more advanced when the excised uterus is examined Therefore, it seems reasonable to insert afterloading Heyman capsules into the uterine cavity of

practically any patient with postmenopausal bleeding when diagnostic dilatation and curettage is performed The risks are low, the radiation exposure to personnel is nil, and there is potential benefit even to some of the presumably favorable cases It is likely that the afterloading principle will increase the indications for the packing procedure particularly in the early or limited cases

The use of preoperative packing of the uterus even in presumed early and favorable stages of endometrial carcinoma would be in accord with the recently reported experience of KJELLGREN & MAGNUSSON (1970)

Conclusions

In the treatment of endometrial carcinoma our afterloading plastic modified Heyman capsules should yield results similar to those achieved with the classical Heyman applicators with the following advantages (1) lessened exposure to radiation personnel and nil to operating room personnel, (2) avoidance of a second operation for patients with endometrial carcinoma for the non radioactive afterloading capsules may be inserted at the time of the original dilatation and curettage (3) more accurate placement of non radioactive capsules and better distention of uterus (4) safer training and teaching of packing procedure (5) opportunity to provide additional experimental data on dose distribution

Acknowledgements

We thank John Boland Professor of Radiotherapy The Mount Sinai School of Medicine for his kind cooperation and help U S patent has been applied for the Simon modification of Heyman capsules by The *Mount Sinai* Hospital Research Foundation

SUMMARY

Packing the uterus for corpus cancer with Heyman applicators containing radium has been useful therapy but the procedure involves unnecessary exposure to radiation It is possible to pack hollow plastic tubes with bulbous ends inside the uterine cavity Subsequently miniaturized radioactive material (^{137}Cs) can be placed in these afterloading tubes decreasing radiation exposure to personnel increasing accuracy of placement and lessening the number of operations requiring anesthesia

ZUSAMMENFASSUNG

Den Uterus zur Behandlung eines Corpus Cancer mit Heyman Applikatoren die Radium enthalten zu füllen ist eine nützliche Therapieform gewesen Das Verfahren ist jedoch mit

einer unnotigen Strahlenexposition verbunden Es ist möglich Plastrohren mit knollien Enden in die Uteruskavitat einzufuhren Nachfolgend in Miniatur nachgebildetes radioaktives Material (^{137} Cs) kann in diese Nachladerohren gefullt werden wodurch die Strahlenbelastung des Personals vermindert wird die Genauigkeit der Lokalisation verbessert und die Anzahl von Operationen die eine Anasthesie verlangen, vermindert wird

RÉSUMÉ

La methode du packing pour le traitement du cancer du corps de l uterus avec les applicateurs de Heyman contenant du radium a ete un traitement utile, mais cette technique comporte une irradiation inutile Il est possible de mettre en place dans la cavite uterine des tubes de plastique creux dont les extremites sont renflées Il est possible de charger ulterieurement ces tubes avec un materiel radio actif miniaturise (^{137} Cs) ceci diminue l exposition du personnel aux radiations améliore la précision de la mise en place et diminue le nombre des operations qui necessite une anesthesie

REFERENCES

CUSBERG S B and COHEN C J Combination therapy for corpus cancer *In* New concepts in gynecological oncology p 237 Edited by G C Lewis Jr W B Wentz and R M Jaffee F A Davis Company Philadelphia 1966

— and YANNOUPOULOS D Therapeutic decisions in corpus cancer Amer J Obstet Gynec 88 (1964) 157

HEYMAN J The so-called Stockholm method and the results of treatment of the uterine cancer of the Radiumhemmet Acta radiol 16 (1935) 129

— REUTERWALL O and BENNER S The Radiumhemmet experience with radiotherapy in cancer of the corpus of the uterus Classification method of treatment and results Acta radiol 22 (1941) 11

KARLSTEDT K Carcinoma of the uterine corpus Factors bearing on curability Acta radiol (1968) Suppl No 282

KJELLGREN O and MAGNUSSON S S Efficacy of primary radiation in carcinoma of the endometrium Acta radiol Ther Phys Biol 9 (1970) 102

KOTTMEIER H L Individualization of therapy in carcinoma of the corpus *In* Collection of papers presented at the Eleventh Annual Clinical Conference on Cancer 1966 at the University of Texas M D Anderson Hospital and Tumor Institute at Houston p 102 Year Book Medical Publishers Chicago 1969

SIMON N Afterloading multiple irradiators for the treatment of cancer of the corpus of the uterus A preliminary report of a new device J Mt Sinai Hosp 36 (1969) 443

FROM THE DEPARTMENT OF RADIOLOGY (DIRECTOR H. O. PETERSON), UNIVERSITY OF MINNESOTA HEALTH SCIENCES CENTER, MINNEAPOLIS, U.S.A.

RADIOACTIVE COBALT TREATMENT OF GLOMUS JUGULARE TUMORS

Clinical and angiographic investigation

by

Y. MARUYAMA, L. H. A. GOLD and S. A. KIEFFER

Radiotherapy and surgery as well as combined radiotherapy and surgery have been used in the therapy of chemodectoma of the jugular fossa. With adequate radiation therapy good local response as well as long term survival results are generally observed (BRADSHAW 1961, CAPPS 1957, GRUBB & LAMPE 1965, MILLER 1966, WILLIAMS et coll. 1955, WILLIAMS 1957). Nevertheless some authors continue to advocate radical excision in preference to radiation. The angiographic examinations reported here were carried out prior to and following radiotherapy to determine the radiation response of the tumor. The radiographic appearance was correlated with clinical symptoms and signs.

The material consists of three cases with histologically proven chemodectomas which were subtotally resected and subsequently treated with radical doses of ^{60}Co therapy.

The tumor and its natural history. The tumor arises from non-chromaffin paraganglion tissue (GUILD 1941, ROSENWASSER 1945) and grows slowly by

This work was in part supported by grants CA08 832, CA05 190 and NB05-422 from the National Institutes of Health. Submitted for publication 17 March 1970.

Table

Treatment of chemodectoma of the jugular fossa by radiotherapy

	Number of responders/ *total number*	Per cent *responders*
WILLIAMS (1957)	12/12	100
FULLER et coll. (1967) Usually biopsy followed by radiotherapy (*including 1—5*	43/43	100
years)	57/57	100
GRUBB & LAMPE (1965) Radiotherapy (alone or following recurrence)	14/14	100
Surgery alone	4/9	44
MILLER (1967)	13/14	93
BRADSHAW (1963)	8/12	75

continuous expansion. The peak incidence is in the 4th or 5th decades and is higher in females than males by three fold (FULLER et coll. 1967). There may be multiple tumors, and rarely it may be malignant (TAYLOR et coll. 1965). The presenting symptoms and signs depend on the site and route of extension of the tumor mass. Symptoms may include a homolateral hearing deficit, pulsatile *tinnitus*, *chronic drainage*, bleeding, ear pain, or those related to cranial nerve deficits (e.g. cranial nerves V, VI, VII, VIII, IX, X, XI, XII). Physical findings may include a mass in the auditory canal, a red and bulging drum, cranial nerve deficits, and bruits over the mastoid process. Half the cases have multiple nerve deficits. Roentgen examinations may reveal erosion or destruction in and around the jugular foramen, *mastoid or deep temporal* region, or sclerosis of mastoid cells. Angiography may demonstrate a highly vascular mass lesion supplied mainly by branches of the external carotid artery. Retrograde jugularography provides information regarding tumor invasion of the jugular fossa (GEJROT 1964) and the venous drainage of the brain.

Case reports and Results

Case 1. White male aged 69 had symptoms of diminished hearing in his left ear for 5 to 6 years which for 18 months had been associated with pulsatile tinnitus. Biopsy of tissue in *the external auditory canal by the referring* physician was associated with *copious* bleeding. Microscopic examination disclosed a chemodectoma. Physical examination revealed deficits of the left *cranial* nerves VII, VIII, X, XI and XII. Decreased air content within the left mastoid cells *and destruction* of the base of the petrous pyramid were seen at roentgen examination. Angiography (Fig. 1a) showed a highly vascular mass lesion of the mastoid. A normal mastoid was found at subsequent mastoidectomy but in the middle



Fig 1 Case 1 Left carotid angiography prior to radiation therapy a) Large ascending pharyngeal artery supplying a vascular tumour in the left temporal bone b) Angiography two years afte radiation therapy A vascular mass in th left temporal bone is still present although the vascularity is slightl reduced

ear region tumor tissue involved the middle ear and tympanum which was partially resected but the procedure was terminated because of excessive bleeding

Following this 5 000 rad of ^{60}Co teleth rapy was given in 30 days by a wedge pair to the left mastoid temporal region Re admission and evaluation at 2 months 9 months and 2 years following radiotherapy showed c plete clinical regression of the auditory canal tumor mass clearing of the ear canal and tinnitus The cranial nerve findings had improved markedly *Angiographic* examination (Fig 1b) continued to show a vascular mass of the jugular fossa although some reduction was evident in the degree of vascularity At the present time *3 years after* therapy tinnitus ontinues to be noticed although of reduced degree and the patient is clinically free of disease

Case White female aged 29 was operated upon for chronic otorrhea 1 year prior to admission Much granulation *tissue was found* in the middle ear at that time Drainage persisted post operatively and she was noted to have a marked hearing deficit Because of persi tent otorrhea she was *again* admitted for further evaluation In addition to an apparent chronic middle ear infection there were homolateral deficits of nerves VIII X X and XII Roentgen examination *revealed sclerosis* and destruction of the mastoid and petrous portions of the left temporal bone Radical mastoidectomy was attempted with the diagn is of chronic recurrent *otitis media* with chronic mastoiditis However profuse and exten ive bleeding interrupted the procedure with blood loss estimated to be 1 ?00 ml

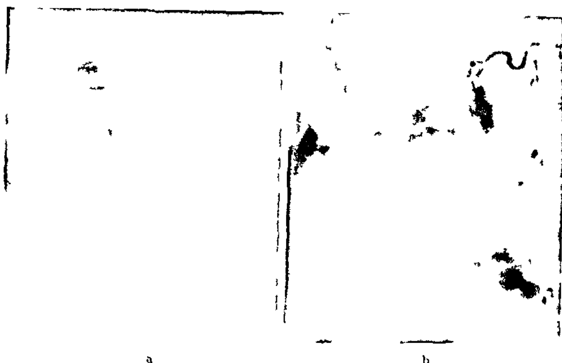


Fig. 2. Case 2. a) Right carotid angiography performed with selective injection into the ascending pharyngeal artery: a highly vascular tumor in the right temporal bone. b) Carotid angiography two years after radiation therapy. The tumor is essentially unchanged from the preirradiation examination.

A chemodectoma was found at histologic examination. Angiography was carried out postoperatively (Fig. 2a) and a highly vascular tumor in the base of the petrous pyramid was found.

^{60}Co teletherapy was carried out using a wedge pair to the left temporal lesion delivering a tumor dose of 5 000 rad in 5 weeks. Repeat angiography was carried out 7 months and 2 years later and continued to show a vascular mass lesion of the petrous apex. During this time the ear canal had cleared, drainage had ceased, tinnitus had improved, and considerable regression of the neurologic findings were noted. Two years later the clinical and neurologic status was stable and most symptoms had cleared. However, angiography continued to show a vascular lesion of the mastoid and jugular fossae. Three years following therapy the external ear canal is clear and symptoms of tinnitus continue. However, angiographically a vascular mass is still present (Fig. 2b).

Case 3. White male, aged 62, developed tinnitus with onset 6 years before admission. There was a gradual onset of difficulties with hearing loss and ear drainage, ataxia, pain in the right eye and right facial weakness. Examination showed weakness of nerves VII, IX, X, XI and XII on the right side, and roentgen examination revealed destruction of the right petrous pyramid. Craniotomy was carried out and a large tumor compressing the brain stem was exposed and partially resected. Extensive bleeding was encountered at surgery. The patient improved for 6 months following surgery but then again deteriorated

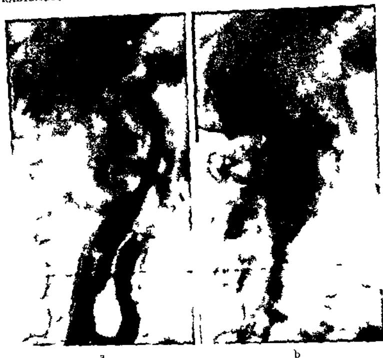


Fig 9 Case 3 a) and b) Pretherapeutic carotid angiography Large external carotid artery branches in the neck and a large highly vascularized tumor involving the right temporal bone and extending down into the soft tissues of the neck

A tarsorrhaphy was required headaches and eye pain worsened staggering and unsteadiness worsened He developed weakness of the right arm and leg

On admission in 1968 the patient was noted to have right sided peripheral facial palsy absent corneal reflex ear deafness absent gag reflex weakness and atrophy of sternomastoid trapezius and atrophy and fasciculation of the right side of the tongue with deviation to the right There was a reddish ulcerated mass involving the right external ear canal with yellowish creamy drainage and a fleshy 3×3×3 cm mass just beneath the right mastoid and external auditory canal A bruit was present in this region In addition he had a right hemiparesis with hyperreflexia of deep tendon and right sided cerebellar signs

Roentgen examination revealed residual contrast medium in the skull and a craniotomy defect There was a destructive lesion of the right petrous bone Angiography revealed a very large vascular mass with accumulation of contrast medium in the region of the right petrous pyramid Numerous tortuous vessels in the upper neck arising from the external carotid were feeding the tumor mass (Fig 9a and b)

^{60}Co teletherapy was delivered to the right posterior fossa ear mastoid and petrous apex and upper neck using a wedge pair 6 000 rad was given in 6 weeks The patient was markedly improved following therapy with clearing of headaches ear canal drainage and



Fig. 4. *Same case as in fig. 3. a) and b) Post-therapeutic angiography.* One and a half years after radiation therapy. The tumor has not significantly changed in size or appearance. The external carotid artery branches are of the same size.

also of his unsteadiness and weakness. In several months he was up and about. The submastoid mass regressed completely. He returned to full activity and is well but continues to have residual nerve weakness as before. Clinical response was considered excellent.

At re-evaluation one and a half years later he was found to be well recovered from the earlier problems. Repeat angiography did not show significant change from the earlier examinations (Fig. 4a and b). Tinnitus continues but the ear canal and neurologic deficits are stable.

Discussion

Capps (1957) has summarized general views on management as follows: "... radical surgery has no present place in the treatment of these cases. The situation and vascularity of the tumors render any surgical approach extremely hazardous." Williams et coll. (1955) state that "surgical procedures should always be combined with radiotherapy". The necessity of a limited procedure for biopsy and establishment of the histologic diagnosis, and for total resection

of only the small easily resectable lesion was stated by ROSENWASSER (1967). Angiography is of value to assess size and extent of the tumor. Radiotherapeutic experience reported by WILLIAMS et coll. (1955), WILLIAMS (1957), FULLER et coll. (1967), GRUBB & LAMPE (1965), BRADSHAW (1959) and MILLER (1966) support the use of radiotherapy (see Table) and in terms of local control, prevention of progression of clinical signs and symptoms, experience indicates that good results were obtained in nearly all cases treated with radiotherapy. Clinical experience (GRUBB et coll. 1965) also indicated that 56 % recurred locally after surgery alone, but no recurrence was observed when radiotherapy was added or used alone. Recurrent tumor after surgery was successfully treated with radiation. Unpublished experience of this clinic also indicate nearly uniform good clinical response using radiotherapy.

To support this experience, histologic evidence of fibrosis and healing of the tumor was presented by ROSENWASSER (1967) and CAPPS (1957) following the use of radiotherapy and indicates that tumor cellularity can be obliterated. Moreover, the results were maintained for long intervals and have been reported for follow up periods extending as long as 32 years (FULLER 1967). FULLER et coll. report Mayo Clinic experience indicating that most cases can be managed by biopsy followed by radiotherapy and that good results are achieved in nearly all cases so managed.

In this study the clinical response of chemodectomas was studied by serial angiography carried out over several years. In each instance clinical response was good. We were therefore surprised to find that despite the excellent clinical response of the patients, there was not a corresponding change in the vascular mass assessed by angiography. Considerable vascularity of similar, albeit of slightly reduced degree continued to be evident. Thus angiographic assessment dissociated from the observed clinical tumor response. Based upon clinical evaluation, additional therapy would not be indicated, and without clear evidence of new activity and clinical signs of progression, the angiographic appearance should not dictate additional therapy. Although the precise mechanism of the tumor response is unknown, the presently described changes suggest that part of the response mechanism may depend on injury to small blood vessels below that of angiographic visibility. However, in addition, the direct effect of radiation in destroying the reproductive and proliferative activity of the neoplastic tumor cells undoubtedly occurs (MARUYAMA 1968).

These studies indicate that other parameters of radiation response can be followed and provide additional information other than that obtained by survival time or mass response. These may be useful for patient evaluation and follow up, however, they may not necessarily correlate with clinical tumor response as was shown by this investigation.

SUMMARY

Serial angiographic examinations were carried out on three cases of glomus jugulare tumors which were treated by high dose ^{60}Co therapy and showed good response by clinical assessment Some decline in size and vascularity was noted however, numerous tumor vessels continued to remain visible for years after therapy The angiographic findings were therefore dissociated from clinical tumor response and should not be regarded as a basis for additional therapy

ZUSAMMENFASSUNG

Serien angiographische Untersuchungen wurden in drei Fällen eines Tumors des Glomus jugulare die mit hohen Dosen ^{60}Co Therapie behandelt wurden und klinisch eine gute Antwort zeigten ausgeführt Ein gewisser Abfall in Grosse und Vaskularität war festzustellen jedoch blieben zahlreiche Tumorgefässe für Jahre nach der Therapie sichtbar Die angiographischen Befunde unterschieden sich somit von der klinischen Tumor Antwort und sollten nicht als Basis für eine weitere Therapie berücksichtigt werden

RÉSUMÉ

Les auteurs ont fait des examens angiographiques en serie dans trois cas de tumeur du glomus jugulaire qui avaient ete traités par de fortes doses de cobalt therapie et presentaient un bon resultat clinique Ils ont constate une certaine diminution du volume et de la vascularisation de la tumeur, cependant de nombreux vaisseaux tumoraux restaient visibles pendant des annees apres le traitement Les resultats angiographiques sont donc dissocies de la reponse clinique de la tumeur et ne devraient pas etre considéres comme un argument pour un traitement complementaire

REFERENCES

BRADSHAW J D Radiotherapy in glomus jugular tumors A review of cases seen at the Christie Hospital from 1943—1959 Clin Radiol 12 (1961) 277

CAPPS F C W Tumors of the glomus jugular and tympanic body J Fac Radiol 8 (1957) 312

FULLER A M BROWN H A HARRISON JR E G and SIEKERT R G Chemodectomas of the glomus jugular tumors Laryngoscope 77 (1967) 450

GEJROT T Jugular syndrome *with special reference to the diagnostic value of retrograde* jugularography Acta oto laryng 57 (1964) 450

GUILD S R Hitherto unrecognized structure the glomus jugularis in man Anat Rec *28 (1941) 79 Abstract No 71*

GRUBB W B and LAMPF I The role of radiation therapy in the treatment of chemodectomas of the glomus jugular Laryngoscope 75 (1965) 1861

MARUYAMA Y Indirect effects in tumor radiation response in vivo A complex role Radiology 91 (1968) 657

MILLER L S Carotid body and glomus jugular *In* Text book of radiotherapy p 245 Edited by G H Fletcher Lea and Febiger Philadelphia 1966

ROSENWASSER H Carotid body tumor of the middle ear and mastoid Arch Otolaryng 41 (1945) 64
— Current management of glomus jugular tumors Ann Otol (St Louis) 76 (1967) 603
TAYLOR D M ALFORD B R and GREENBERG S D Metastases from glomus jugular tumors Arch Otolaryng 82 (1965) 5
WILLIAMS H L CHILD D S PARKHILL E M and PUGH D G Chemodectomas of the glomus jugular (non-chromaffin paragangliomas) with especial reference to their response to roentgen therapy Ann Otol (St Louis) 64 (1955) 546
WILLIAMS I G Radiotherapy of tumors of glomus jugulare J Fac Radiol 8 (1957) 335

FROM THE DEPARTMENTS OF RADIOLOGY AND SURGERY, MEDICAL COLLEGE OF VIRGINIA, RICHMOND, VIRGINIA, U S A

RADIATION FOR IMMUNOSUPPRESSION IN HUMAN ORGAN TRANSPLANTATION

I Experimental data

by

S H LEVITT, F T O'FOGHLUDHA, R L ROYSTER, J S WOLF, R R LOWER and L S DEGIORGI

The replacement of diseased or worn out parts or organs has intrigued man for centuries. Mention is made in Greek mythology of transplants from animal to man, and early Christian legends and folk tales tell of successful transplants of noses and limbs from one individual to another. In the middle ages physicians and lay literary figures repeatedly considered in their treatises the possibility of transplantation of a structure from one individual to another.

Probably the first successful clinical transplant in modern history was reported in 1823 by BUNGER (*the historical information in this section was treated in detail by* CONVERSE & CASSON in 1968) who reconstructed part of a woman's nose by a free graft from her thighs. As early as the middle of the 19th century the difference between the behavior of autografts, allografts and xenografts was recognized by BECK, one of the early workers in transplant research.

The types of tissue transplants are given below

Autochthonous (autologous)	*Individual's own tissues*
Syngeneic (isologous)	Identical twins, animal inbred strain
Allogeneic (homologous)	Same species
Xenogeneic (heterologous)	Different species

Submitted for publication 11 May 1970

The idea that allograft rejection is mediated by a process of active immunity is attributed to JENSEN (1903) Further work to verify this concept was done by many other investigators The first organ transplant was reportedly done by BECK in Chicago in 1903 at which time he transplanted an experimental kidney Further developmental transplantation approaches were carried out by CARREL FLORESCO DECLEVERS and others

The basic concepts concerning the reaction of a host to transplantation of tissue from another unrelated individual were first formulated by investigators in the field of tumor research early in the 20th century The hypothesis of the immune response was one of those proposed to explain the rejection phenomenon and was expounded by RUSSEL and MURPHY MURPHY concluded from a series of experiments utilizing transplanted tumors that the defense mechanism responsible for the destruction of the transplant was centered in the small lymphoid cell He later attempted to modify the rejection process by interference with the function of the lymphocyte through irradiation and the administration of benzoyl Despite this work there remained much disagreement about the role of immune respon e in the allogenic tissue transplant reaction until the mid 1940 s In 1944 MEDEWAR carried out the basic experiments which led to the recognition of the role of the immune response in transplant rejection and incidentally to further exploration of the role of radiation in the suppression of this response

The basic problems in organ transplantation have been and are the technical factors involved in organ transplant pre ervation and the prevention of the rejection phenomenon This paper will deal with the role of radiotherapy which is primarily that of preventing rejection in organ transplantation

Types of rejection

Rejection of organ transplants is classified under three headings hyperacute acute and chronic

Hyperacute reactions occur within minutes or a few hours after the organ has been tran planted and are very similar in timing to second set transplant rejections Changes in the organ may frequently be observed before completion of the transplant operation These include blood vessel destruction hemorrhage and thrombosis (WILLIAMS et coll 1968) This immediate reaction is mediated by humoral antibodies present in the recipient prior to the transplant surgery These antibodies may develop as a result of pregnancies blood transfusions previous tran plants or in certain instances bacterial infection

Acute rejection occurs within a few weeks and up to about four months following tran plant This reaction is the classical primary response of cellular immunity which proceeds in ome patients regardless of the method of immuno

FROM THE DEPARTMENTS OF RADIOLOGY AND SURGERY, MEDICAL COLLEGE OF VIRGINIA, RICHMOND, VIRGINIA, USA

RADIATION FOR IMMUNOSUPPRESSION IN HUMAN ORGAN TRANSPLANTATION

I Experimental data

by

S H LEVITT, F T O FOGHLUDHA, R L ROYSTER, J S WOLF,
R R LOWER and L S DEGIORGI

The replacement of diseased or worn out parts or organs has intrigued man for centuries Mention is made in Greek mythology of transplants from animal to man, and early Christian legends and folk tales tell of successful transplants of noses and limbs from one individual to another In the middle ages physicians and lay literary figures repeatedly considered in their treatises the possibility of transplantation of a structure from one individual to another

Probably the first successful clinical transplant in modern history was reported in 1823 by BUNGER (the historical information in this section was treated in detail by CONVERSE & CASSON in 1968) who reconstructed part of a woman s nose by a free graft from her thighs As early as the middle of the 19th century the difference between the behavior of autografts allografts and xenografts was recognized by BECK one of the early workers in transplant research

The types of tissue transplants are given below

Autochthonous (autologous)	Individual s own tissues
Syngeneic (isologous)	Identical twins, animal inbred strain
Allogeneic (homologous)	Same species
Xenogeneic (heterologous)	Different species

Submitted for publication 11 May 1970

Present methods of immunosuppression

Immunosuppressive agents such as steroids radiation and antimetabolites together with antilymphocyte serum and globulin have been used alone or in various combinations to suppress the immune response in man

All the measures commonly used today depend upon the destruction of the lymphocyte and suppression of new lymphocyte production or at least deactivation of its role in the immune response Since humoral immunity against the transplanted organ also develops and free antibodies may be present the antilymphocyte actions of prednisone azathioprine antilymphocyte globulin or radiation may not be completely effective

The chemotherapeutic agents used most commonly are prednisone and azathioprine The routine daily doses given post transplant are 3 to 4 mg/kg of azathioprine and 5 to 60 mg of prednisone depending upon graft acceptance

Radiation has been used in various ways and with various do es Radiation acts to destroy the lymphocytes that are present and to suppress new production, thus interfering with their role in the launching of the rejection process in allotransplanted tissue The small lymphocyte is very sensitive to radiation, the D_0 for all proliferating hematopoietic cells is about 100 rad and it has been shown that doses as small as 12 to 50 rad can destroy a fraction of the lymphocytes

Methods of irradiation

Total body irradiation

The purpose of total body irradiation is to suppress all immune mechanisms Total body irradiation in doses sufficient to suppress humoral immune respon e substantially or to increase the acceptance of allografts results in an almost complete loss of the small lymphocytes and destruction of germinal centers in the lymph nodes and spleen The population of small lymphocytes in the bone marrow dimini hes along with the other cell lines

A Supralethal irradiation with bone marrow transplantation Irradiation of the host prior to transplant in order to prevent rejection requires doses in man which have been incompatible with survival for the most part

B Sublethal total body irradiation This has not been successful in most animal experiments unless immunosuppressive agents are also used In man it has been used in the first four kidney transplants at our institution two of the patients later died and two are still alive Because of the dangers inherent in this approach it has been abandoned

Local irradiation

The purpose of local irradiation is to depress immune response and lymphocytes locally and to avoid the reaction inherent in total body irradiation

suppression used An infiltration by monocytes is the first demonstrable pathologic phenomenon and *occurs within 24 to 48 hours Endothelial* cellular damage, interstitial edema, and round cell infiltration, tubular necrosis and occlusion of vessels and decreased renal blood flow, are regular features of acute rejection

It is believed by most authorities that the small lymphocyte is responsible for acute rejection The role of the lymphocytes in the process is hypothesized as follows small circulating lymphocytes, called immunologically competent small lymphocytes (ICSL), react with the challenging antigen and migrate via afferent lymphatics to the lymph nodes (this phase is sometimes referred to as the afferent arc) In the lymph nodes *these lymphocytes become fixed in lymphatic* tissue and differentiate into large pyroninophilic cells which go through a number of divisions and result in the production of plasma cells or new small lymphocytes These new cells are also called the immunologically activated small lymphocytes (IASL) These activated cells migrate in time to the graft and in some manner, not yet completely understood, destroy the graft tissue (this phase is called the efferent arc)

The possible methods of action (CRONKITE & CHANANA 1968) of these sensitized cells in the graft are (1) having antibody like structures bound into them, acting directly on target cells, (2) releasing a humoral antibody in high concentration near the cells, (3) carrying a cytophilic antibody, (4) acting as phagocytic scavengers after the graft has been opsonized by *humoral antibody circulating* in the plasma, and (5) releasing enzymes which damage both graft and host cells

Chronic rejection occurs after about four months, and in certain instances as long as four years It is seen in patients on immunosuppressive therapy and may demonstrate a partially successful attempt at immunosuppression Cellular infiltration is absent, and histologic changes occur in the basement membrane of the glomerulus and the endothelium of small blood vessels Endothelial proliferations *is observed with narrowing and* ultimate occlusion of the lumina of vessels Damage to glomerular capillaries leads to protein loss in the urine, a slow rise in blood urea nitrogen (BUN) and serum creatine and a decline in glomerular *filtration and renal plasma flow This rejection phenomenon is* apparently produced by circulating humoral antibodies (immunoglobulins) These antibodies have been detected in man following removal of kidney allografts (HUME & WOLF 1967)

At present, only the acute form of rejection can be practically controlled although a great amount of research is going into attempts to control the hyperacute and chronic types The role of irradiation (and indeed all other forms of immunosuppressive therapy used at this time) is to suppress the acute form of rejection

the second transplant was done This second transplant was also rejected but not as rapidly The difference in survival was significant This showed that irradiation had partially interfered with immunization of the host

That local irradiation is also useful in reducing heart rejection in dogs has been shown by LOWER and associates (GRAHAM et coll 1970 LOWER et coll 1968) who studied fifteen animals that had undergone successful cardiac allo transplantation All dogs received a course of azathioprine for the first three days post transplant and were treated with ^{60}Co gamma rays through 10 × 12 cm portals while lying on their right sides Various do e schedules were used (see below) all doses being calculated at 6 cm depth in the para axillary area The electrocardiogram was monitored daily in all animals Acute rejection was diagnosed if the QRS voltage fell to one half or less of the maximum post operative level while the response was considered favorable if the voltage returned to normal or nearly normal values At the completion of the irradiation open biopsy of the left ventricle was carried out in all animals and light and electron micro copic investigations were performed

Two groups of animals were studied Group 1 consisted of three dogs receiving 450 rad in three equal consecutive daily fractions, one dog which received 600 rad in four such fractions and one which received 900 rad in six fractions Only one animal in this group showed any electrocardiographic response to irradiation and none showed any improvement microscopically

In Group 2 the total dose was considerably larger (1 500 rad in 300 rad frac tions given on five consecutive days) than in Group 1 Six of ten animals treated at this larger dose level responded to radiation as demonstrated both in the ECG and histologically In five of the six animals which improved there was marked decrease in the degree of cellular infiltration interstitial edema and congestion and there was less endothelial cell swelling and necrosis Ultrastructurally the outstanding change was in the myocytes Prior to radiation these cells had a smudgy and disoriented appearance the transverse bands were frequently in distinct and the mitochondria were swollen and vesicular and myelin figures and lipid droplets were readily apparent There was hypertrophy of the en dothelium of the vessels with interstitial edema and monocyte infiltration Fol lowing irradiation the myocytes appeared more normal were less disoriented and the transverse bands were more distinct The mitochondria endoplasmic reticulum and transverse tubular system were also less vesicular swelling of the endothelium in the small blood vessels was less marked and there was le s cellular infiltration of the interstitium

The experiment is most noteworthy since this is the first time that the thera peutic effect of radiation on acute rejection has been documented histologically The study also seems to demonstrate that in order to prevent rejection of heart

1 Irradiation of the site prior to transplant In skin grafts, the antigen sensitive lymphocytes drain from graft site to the local nodes for ICSL development so that irradiation of these areas leads to prolonged skin graft survival However, local kidney transplants do not necessarily depend upon regional lymphatics or lymph nodes for ICSL development and irradiation of the graft site prior to kidney transplant is not effective This difference in route of sensitization was shown in the surgical laboratories of the Medical College of Virginia where complete isolation of a kidney transplant from regional, lymphatic drainage did not prolong survival (HUME et coll 1963) WOODRUFF et coll (1963) also found that irradiation of the graft site prior to transplant in human renal transplants was not effective in preventing rejection

B External irradiation of the transplant BANKS et coll (1961) found that local irradiation in kidney transplants of dogs did not prolong functional survival when doses of up to 770 rad were given in daily fractions of 100 rad KAUFFMAN et coll (1965) found that 150 rad was the smallest individual dose capable of preventing homograft rejection, this was most effective when given on the day of transplant A dose of 200 rad given on the initial day appeared to be less effective in prolonging graft survival The possible mechanisms are

Alteration of graft antigenicity is not likely since single doses as high as 1500 rad to dog kidneys prior to transplant did not decrease the antigenicity

Alteration of graft bed and adjacent lymphatics may be a factor in prevention of skin graft rejection but not in kidney grafts because of the difference in afferent and efferent pathways in the two situations

Alteration of graft versus host activity It has been theorized that local irradiation might act to decrease graft versus host reaction However, FOWLER & PORTER discount this idea since they have definitely shown that the cells infiltrating the kidney are of host origin (CRONKITE & CHANANA 1968)

Local non specific anti inflammatory effect

Interference with the afferent and efferent arcs Radiation destroys the sensitized host lymphocytes invading the transplant, thereby interfering with the efferent arc rejection and thus leading to prolonged graft survival This has been confirmed by experiments in which two kidneys from a single donor were placed into a single recipient One kidney was irradiated and the other was not and the survival was significantly greater in the irradiated kidney

Local roentgen irradiation to the transplant is also capable of affecting the afferent arc of the immune response In another series of experiments involving second transplants from the same donor into the same recipient, a series of dogs were immunized by a kidney transplant followed a week later by a second transplant The second transplant was rejected in an accelerated manner In another series of dogs the first transplant was irradiated Following rejection of this kidney

least one model is commercially available the Departments of Radiology and Surgery at our institution have collaborated in producing and testing several successful devices one of which is a wrist borne bracelet containing a coil of thin walled plastic tubing attached to an a v shunt near the wrist (O FOGHLUDHA & WOLF 1968) Curved plates incorporating sealed ^{90}Sr sources bear against the coil and transfer approximately one quarter of the radiated energy to the blood traversing the tubing The device is completely portable and may be worn by the patient for periods long enough to insure that the blood dose is reasonably uniform There is no appreciable external hazard (O FOGHLUDHA) provided the containers remain intact The device can be worn by an ambulant patient who must however stay in the hospital The current device can deliver a mean dose of approximately 1 000 rad/day to patients of normal blood volume A pilot irradiator relying on ^{32}P has also been constructed and further work continues (O FOGHLUDHA)

Experimentally the beta ray method has been shown to prolong renal homograft functional survival in humans most effectively when irradiation is begun immediately after transplantation (O FOGHLUDHA)

E Lymphatic or reticulo endothelial cell irradiation CRONKITE & CHANANA studied the effect of thoracic duct lymph irradiation on skin graft placed so that they drained almost entirely into the thoracic duct Skin grafts placed in other areas so that the lymphatic drainage was not solely to the thoracic duct did not show the same increased survival The authors felt that this phenomenon demonstrated a radiation effect on the afferent arc in the graft placed close to the thoracic duct and showed interference with specific graft antigen The less significant prolongation in the grafts non adjacent to the thoracic duct was felt to be due to general lymphocyte depletion

HAHN et coll attempted to prolong renal homograft survival in dogs with intravenous injections of ^{198}Au but this was unsuccessful The same substance in colloidal forms has also been infiltrated directly into the lymphatics and similar experiments have been made with Bi ^{111}Ag ^{90}Y ^{32}P and ^{131}I tagged ethiodol or antigen Success has been variable and the method is not practical in clinical use (HUME & WOLF 1967)

F Irradiation of thymus and spleen Theoretically this method should decrease the ICSL population No benefit has however been found in renal allograft prolongation in numerous studies and the method has been abandoned

SUMMARY

Organ transplantation and the phenomenon of rejection and its prevention are discussed The role of radiation is specifically discussed based on animal kidney and heart transplants performed at the Medical College of Virginia

transplants higher dose levels of irradiation are needed than in the case of kidney grafts

C Internal radiation of the graft using isotopes WILLIAMS & SCHAPIRO gave dogs radioactive chlormedrin ^{203}Hg intravenously and noted prolonged survival of renal homografts when doses of approximately 85 to 160 rad per day were delivered by the material The difficulties of controlling localization and dose are obvious, and this approach does not appear to be useful in man

D Blood irradiation Irradiation of the circulating blood has been utilized to produce generalized lymphopenia and thereby diminish homograft rejection by decreasing ICSL without the reactions of total body irradiation

Irradiation of an artery leading to the renal homograft At the surgical laboratories of the Medical College of Virginia a skin pedicle was created in the neck of a dog and the carotid artery was incorporated in it Next, a renal transplant was carried out and the distal end of the carotid skin pedicle was anastomosed to the new artery of the transplanted kidney The carotid artery was then irradiated by a shielded radiation source There was subsequent prolongation of renal homograft survival Since a generalized lymphopenia was also produced, it may be that although only the blood to the transplant had been irradiated, enough of the blood volume had been irradiated to produce a general extracorporeal irradiation rather than selective irradiation of blood entering the kidney

Intra arterial implants Implantation of silastic coated pellets of ^{90}Y into the center of the abdominal aorta of dogs prolonged renal homograft survival in our laboratories Serial histologic sections of the spleen and mesenteric lymph nodes showed progressive depletion during the radiation period

Extracorporeal blood irradiation CRONKITE & CHANANA demonstrated prolongation of skin homografts using an extra corporeal shunt exposed to ^{60}Co gamma rays Although this method is quite effective, the heavy shielding required makes the equipment very cumbersome

Shunt irradiators incorporating pure beta emitters such as ^{90}Sr or ^{32}P have the advantage that the necessary shielding is very much lighter because the beta particles have low penetrating power This otherwise advantageous property of the beta rays is, however, a drawback if irradiation of large blood volumes is attempted because only those portions of the blood passing very close to the radiation source receive any energy from it When the volume of blood instantaneously irradiated is small, as dictated by this last limitation, prolonged irradiation becomes necessary in order to achieve any substantial uniformity of dose, because a given cell passes through the shunt at irregular intervals and a wide distribution of cell doses therefore occurs for the shorter exposure time (O FOGH LUDHA 1969)

Suitable beta irradiators have been constructed in several laboratories and at

least one model is commercially available the Departments of Radiology and Surgery at our institution have collaborated in producing and testing several successful devices one of which is a wrist borne bracelet containing a coil of thin walled plastic tubing attached to an a v shunt near the wrist (O FOGHLUDHA & WOLF 1968) Curved plates incorporating sealed ^{90}Sr sources bear against the coil and transfer approximately one quarter of the radiated energy to the blood traversing the tubing The device is completely portable and may be worn by the patient for periods long enough to insure that the blood dose is reasonably uniform There is no appreciable external hazard (O FOGHLUDHA) provided the containers remain intact The device can be worn by an ambulant patient who must however stay in the hospital The current device can deliver a mean dose of approximately 1 000 rad/day to patients of normal blood volume A pilot irradiator relying on ^{3} P has also been constructed and further work continues (O FOGHLUDHA)

Experimentally the beta ray method has been shown to prolong renal homograft functional survival in humans most effectively when irradiation is begun immediately after transplantation (O FOGHLUDHA)

E Lymphatic or reticulo endothelial cell irradiation CRONKITE & CHANANA studied the effect of thoracic duct lymph irradiation on skin graft placed so that they drained almost entirely into the thoracic duct Skin grafts placed in other areas so that the lymphatic drainage was not solely to the thoracic duct did not show the same increased survival The authors felt that this phenomenon demonstrated a radiation effect on the afferent arc in the graft placed close to the thoracic duct and showed interference with specific graft antigen The less significant prolongation in the grafts non adjacent to the thoracic duct was felt to be due to general lymphocyte depletion

HAHN et coll attempted to prolong renal homograft survival in dogs with intravenous injections of ^{198}Au but this was unsuccessful The same substance in colloidal forms has also been infiltrated directly into the lymphatics and similar experiments have been made with ^{6}Bi ^{111}Ag ^{90}Y ^{3} P and ^{131}I tagged ethiodol or antigen Success has been variable and the method is not practical in clinical use (HUME & WOLF 1967)

F Irradiation of thymus and spleen Theoretically this method should decrease the ICSL population No benefit has however been found in renal allograft prolongation in numerous studies and the method has been abandoned

SUMMARY

Organ transplantation and the phenomenon of rejection and its prevention are discussed The role of radiation is specifically discussed based on animal kidney and heart transplants performed at the Medical College of Virginia

ZUSAMMENFASSUNG

Organ Transplantationen und die Erscheinung der Abstossung und deren Verhinderung werden besprochen. Auf die Bedeutung der Bestrahlung wird eingehend mit Hinblick auf Nieren- und Herztransplantationen, die an der Medizinischen Hochschule von Virginia bei Tieren ausgeführt wurden, eingegangen.

RÉSUMÉ

Les auteurs étudient la transplantation d'organe, le phénomène de rejet et sa prévention. Ils étudient le rôle des radiations en se basant sur les greffes de rein et de cœur d'animaux faites au Medical College de Virginie.

REFERENCES

To be given in part II of this paper.

FROM THE DEPARTMENT OF TUMOR BIOLOGY THE MEDICAL SCHOOL OF KAROLINSKA INSTITUTET, STOCKHOLM, SWEDEN

RADIATION DAMAGE AND REPAIR IN CYSTEAMINE TREATED CELLS

by

B LITTBRAND and I RÉVESZ

Preliminary experiments (RÉVESZ 1969 RÉVESZ & LITTBRAND 1970) have suggested that cysteamine treatment modifies both parameters of the survival curves of irradiated cells i e the slope and the extrapolation number These observations were interpreted as indicating that the effect of cysteamine concerns the production of radiation damage as well as its repair MAURO et coll (1969) have recently arrived at a similar conclusion

The recovery from radiation damage has been shown to be an energy requiring cellular process dependent upon the availability of oxygen during irradiation (ASHBY & BONTE 1968 BRYANT 1968, HOWARD 1968, KEMBER 1967 LITTBRAND & RÉVESZ 1969 PHILLIPS 1968) On the other hand preliminary data indicated that cysteamine treatment permits recovery even when oxygen is absent during and present only after irradiation The hypothesis was therefore put forward that cysteamine may *influence the* repair process by prolonging the period of recovery of the radiation damage before it becomes irreversibly fixed This paper describes the experiments performed to test this hypothesis

Submitted for publication 26 February 1970

ZUSAMMENFASSUNG

Organ-Transplantationen und die Erscheinung der Abstossung und deren Verhinderung werden besprochen. Auf die Bedeutung der Bestrahlung wird eingehend mit Hinblick auf Nieren- und Herztransplantationen, die an der Medizinischen Hochschule von Virginia bei Tieren ausgeführt wurden, eingegangen.

RÉSUMÉ

Les auteurs étudient la transplantation d'organe, le phénomène de rejet et sa prévention. Ils étudient le rôle des radiations en se basant sur les greffes de rein et de cœur d'animaux faites au Medical College de Virginie.

REFERENCES

To be given in part II of this paper.

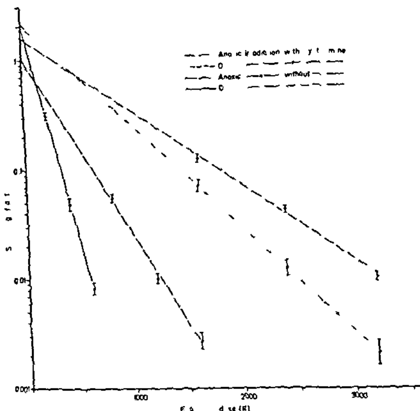


Fig 1 Survival curves of cysteamine treated or untreated Chinese hamster cells irradiated under oxic or anoxic conditions The mean surv val regressions were calculated by least square analysis of the data in 6 to 10 separate tests Vertical bars denote the standard error of th mean survi ing fraction The numerical value of the survival parameters are presented in Table 1

chamber or left there and exposed for varying post irradiation conditions When removed the cells were washed three times with a balanced salt solution re fed with fresh medium and subsequently incubated under aerobic conditions for a period of 8 to 10 days with one medium change on the 2nd and 3rd day When left in the chamber the post irradiation conditions were varied either by clo ing the chamber hermetically and leaving the cells in the cysteamine con taining medium under anoxic conditions or by introducing air into the chamber without any change of the cysteamine containing medium or by introducing air and after the cells were washed changing the medium to one that contained no cysteamine The post irradiation conditions were maintained for 1 or 2

Table 1

Numerical values of the survival parameters presented in Fig. 1

Atmosphere during exposure	Cysteamine concentration (mM)	Number of repeat tests	Plating efficiency Mean ± S.E. (per cent)	Slope constant of survival regression Mean ± S.E.* (^{e}log units/100 R)	D_0** Mean (R)	Extrapolation number*** Mean ± S.E. (^{e}log units)	Extrapolation number*** Arithmetic value of mean
Anoxic	20	10	72 ± 5	−0.157 ± 0.005	636	0.447 ± 0.013	1.56
Anoxic	0	10	74 ± 5	−0.369 ± 0.020	271	−0.040 ± 0.086	0.96
Oxic	20	8	69 ± 4	−0.215 ± 0.012	466	0.731 ± 0.014	2.08
Oxic	0	6	64 ± 9	−0.885 ± 0.090	113	0.632 ± 0.076	1.88

* *Calculated from the regression coefficients which were determined by least square analysis of the survival data in each test separately.*

** Reciprocal of the mean regression coefficient.

*** Intersection of the regression line with the ordinate at zero R.

Materials and Methods. A Chinese hamster cell line, V79-379 A, was used as the cell material propagated under standard tissue culture conditions. The nutrient medium consisted of Eagle's medium in Earle's saline (EAGLE 1959) supplemented with 15 % fetal calf serum and antibiotics. For each experiment monodispersed cells were prepared from 6 to 8 day old cultures by treatment with 0.5 % trypsin solution. The cells were explanted in pre-determined numbers in Pyrex petri dishes. After 2.5 to 3.5 hours incubation in air with 5 % carbon dioxide, cysteamine was added to the medium in 20 mM concentration. Control cultures received no cysteamine. As indicated by the data in Table 1, cysteamine had no toxic effect on the plating efficiency of the cells at the concentration used. Fifteen minutes later, the medium was drained to such an extent that no more than 1 ml was left in the dishes covering the cells with an average fluid layer of less than 0.4 mm. Exposure to radiation was then made in an air tight plastic chamber of 2 liter volume. The chamber was flushed before and during the radiation exposure for a period of at least 7 minutes at a rate of 6 liter/minute with either argon containing less than 2 ppm oxygen or air to create anoxic and oxic conditions, respectively. Carbon dioxide was routinely added to the gases to maintain a pH of 7.2 in the medium. A detailed description of the system for the control of the gaseous condition during irradiation has been published (LITTBRAND & REVESZ 1969). After irradiation, the cells were either removed immediately from the radiation

determined after exposure to three different doses Those chosen were of such a magnitude as to decrease the surviving fraction to comparable levels in the range between 10^{-1} and 10^{-2} The curves each determined from the mean of 8 to 10 repeat tests are illustrated in Fig 1 For comparison data obtained in a previous study (REVESZ & LITTBRAND 1967) in which cells untreated with cysteamine were exposed oxically are also included

It will be noted that cysteamine changed the survival regression of the anoxically as well as the oxically irradiated cells As may be calculated from the numerical value of the parameters presented in Table 1 the D_0 value of the anoxically irradiated cells increased by a factor of 2 4 due to the presence of cysteamine during irradiation A factor of 4 1 may be calculated for the D_0 increase in the case of the oxic exposures

The extrapolation number (n) of the anoxic survival curves was also raised by the cysteamine treatment The factor was then 1 6 No significant increase of n occurred however when oxic conditions prevailed during irradiation

Cysteamine treated cells in another series of experiments were exposed to a single radiation dose or the same dose divided into two fractions under oxic or anoxic conditions The surviving fractions and the split dose ratios were calculated in each of 12 to 24 repeat tests The means are illustrated in Fig 2 Data from previous tests in which the cells were exposed oxically without any cysteamine treatment are also presented for comparison (LITTBRAND 1970) Due to the cysteamine treatment the mean split dose ratio increased by a factor of 1 5 when anoxic conditions prevailed during irradiation The split dose ratio of cysteamine treated cells differed however only slightly from the split dose ratio of untreated cells when exposures were made oxically

The effect of split dose treatment as against single dose treatment was investigated after various post irradiation conditions in a third series of experiments Cysteamine treated cells were exposed to 3 200 R or the same dose split into two fractions under anoxic conditions The anoxic conditions were maintained in some of the tests for 1 hour (Group A) or 2 hours (Group B) after irradiation and before the cells were incubated aerobically Cysteamine was left in the medium during this period In other tests aerobic conditions started immediately after irradiation The cysteamine medium in the latter was removed simultaneously and exchanged for fresh medium (Group C) or alternatively was left to cover the cells for an additional 2 hours (Group D) The results are presented in Table 2

The surviving ratio in the experiments in which cysteamine was removed from the medium and the cells had access to oxygen immediately after treatment (Group C) had a similar value as the ratio in the comparable experiments presented in Fig 2 A similar split dose ratio was also calculated when

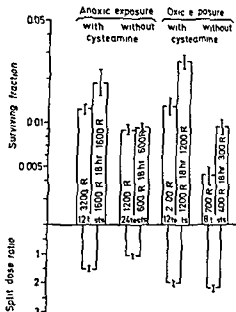


Fig 2 Survival of cysteamine treated or untreated Chinese hamster cells after oxic or anoxic exposures to single or split doses of radiation (upper scale) The ratio of the survival after a single dose to the survival after split doses as calculated from the split dose ratio in each of the tests is also shown (lower scale) The columns represent the mean with standard error and indicate also the radiation dose number of tests and interval between split doses The mean plating efficiency in these experiments varied between 64 and 80 per cent

hours The cells were then removed from the chamber, the cysteamine containing medium changed to fresh medium without cysteamine, and the cultures incubated aerobically for about 10 days

When radiation doses split into two fractions were given the procedure was repeated at both exposures The cells were incubated aerobically during the time interval between the irradiations which always lasted for 18 hours Cultures that received the total dose at a single exposure were sham irradiated under identical conditions Clones that developed after incubation of the cultures were fixed and stained in situ The mean number of clones was established by counting three dishes, clones comprising less than 50 cells were not included The fraction of cells that survived irradiation was expressed as the percentage of the sham irradiated controls in the same experiment

A Siemens roentgen unit was operated at 190 kV and 15 mA, the radiation was filtered by 1 5 mm Al inherent filtration and a 1 0 mm Al additional filter, giving 0 95 mm Cu HVL The dose rate was 235 R/minute at the bottom of the culture dishes at a distance of 43 cm from the focus A Philips integrating dosimeter was routinely used for the dose measurements

Results

The effect of cysteamine in 20 mM concentrations was investigated on the survival parameters of Chinese hamster cells exposed to radiation in the presence or absence of oxygen in a series of experiments The survival curve was always

Table 2 (*cont*)

Percentage survival Mean±S E (ᵉlog units)		Survival ratio	
Single dose *exposure*	Split dose exposure	Mean±S E (ᵉlog units)	Arithmetic value of *the mean*
−0 009±0 214	0 278±0 224	0 287±0 06?	1 33
0 099±0 059	0 162±0 058	0 063±0 016	1 07
0 282±0 075	0 710±0 077	0 428±0 0?7	1 53
0 099±0 073	*0 504±0 079*	0 405±0 0?3	1 50

reasonable agreement with *comparable data reported* by VERGROESEN et coll (1967) and obtained in their experiments with another cell type The present results are, furthermore also in agreement with previous considerations (BACQ 1965) according to which the cysteamine effect is due not only to the induction of cellular resistance indirectly by decreasing oxygen tension but also to some direct protection by the substance The protection manifested in a decrease of the slope of the survival regression, may be considered to express a decrease of damage production by *radiation* The *increase* in the extrapolation number or split dose ratio should be regarded as expressing a protection by cysteamine due to the repair of the radiation damage already produced

An *increase* in the extrapolation number and a similar increase in the split-dose ratio were recorded in the present *experiments* when cysteamine treated cells were irradiated anoxically this indicated a certain cellular recovery *from* radiation injury Recent data (ASHBY & BONTE 1968 BRYANT 1968, HOWARD 1968 LITTBRAND & REVESZ *1969*) *suggest* that recovery from sublethal injury may be an active energy requiring metabolic process *dependent upon* oxidative metabolism Since fully aerobic conditions even shortly after anoxic irradiation fail *to restore* recovery it has been concluded that the period during which the radiation injury is recoverable may be short (LITTBRAND & REVESZ 1969) It is conceivable that the injury becomes rapidly fixed unless the recovery process dependent upon the available energy sources in due course interferes An analogous situation may exist in connection with the repair of radiation induced chromosome breaks (WOLFF & LUIPPOLD 1955, 1958)

The recovery observed after anoxic radiation exposures cannot therefore be

Table 2

Effect of varying post irradiation conditions on the survival ratio of cysteamine treated and anoxically irradiated cells Irradiations were always made with a single exposure dose of 3 200 R or with the same dose split into two equal fractions separated by an interval of 18 hours

Group	Number of repeat tests	Post irradiation conditions			Plating efficiency Mean±S E (per cent)
		Atmosphere	Cysteamine	Duration	
A	5	Anoxic	Present	1 hour	65±5
B	20	Anoxic	Present	2 hours	62±3
C	15	Oxic	Absent	2 hours	63±3
D	5	Oxic	Present	2 hours	71±4

* Ratio between the surviving fractions after treatment with single and split doses
** Calculated from the survival ratios determined for each test separately

cysteamine was left in the medium during the aerobic post irradiation period (Group D) The survival ratio decreased, however, under anaerobic post irradiation conditions and with cysteamine left in the medium The decrease was slight at 1 hour (Group A), but the split dose ratio was close to unity at 2 hours (Group B)

Discussion

The results indicate that cysteamine treatment modifies the survival regression as well as the recovery of irradiated cells The data indicating the change of the survival regression of the oxically irradiated cells are in reasonable agreement with the observation SINCLAIR (1969) made in experiments with another Chinese hamster cell line, and with the findings of VERGROESEN et coll (1967) in their experiments with human kidney cells On the other hand, MAURO et coll (1969) calculated modifying factors not exceeding 2 in their experiments with HeLa and Chinese hamster cells This value is considerably lower than the values found in the present experiments and the experiments referred to above

Cysteamine decreased the survival regression of anoxically irradiated cells by a factor of 2 4 The modifying effect of cysteamine when irradiation is delivered under oxic conditions, is expressed by a factor of 4 1, i e it is considerably larger than the ratio for the oxygen enhancement When the survival regression of the oxically irradiated and cysteamine untreated cells is related to the regression of anoxically irradiated, cysteamine treated cells, a factor of 5 6 can be calculated These factors, although they have slightly larger values, are in

value increased by a factor of 4 1 but the extrapolation number failed to change significantly

Exposure of cysteamine treated cells to split doses increased the survival by a factor of 1 5 in comparison to the survival after a single exposure to the same total dose when anoxic conditions prevailed during the irradiations No similar increase in the survival of the untreated cells was noted When oxic conditions were maintained during irradiations exposure to split doses increased the survival of both the cysteamine treated and untreated cells by a factor of about 2 in comparison to a single exposure to the same total dose

When the anoxic conditions during the exposures were maintained for 1 hour after irradiation and before the aerobic incubation of cells the cysteamine induced increase of the split dose survival was lower than when aerobic conditions followed immediately Only a slight increase of the split dose survival was noted when the anoxic conditions were maintained for 2 hours

The data are consistent with the assumption that cysteamine prolongs the time period during which the radiation damage remains recoverable and before it is fixed irreversibly

Acknowledgements

The authors wish to thank Mrs Ingegerd Hedlof and Miss Rut Jonsson for their *technical* assistance The work was supported by grants from the Swedish Cancer Society the *Sir Samuel Scott of Yews Trust* and the International Atomic Energy Agency

SUMMARY

The effect of cysteamine on the survival parameters of oxically or anoxically irradiated Chinese hamster cells was investigated The results suggest that cysteamine treatment decreases the production of radiation damage and at the same time contributes to repair of such damage

ZUSAMMENFASSUNG

Zellgewebe des chinesischen Hamsters wurde benutzt um den Effekt des Cysteamins auf die Überlebungsparameter nach Bestrahlung unter sauerstoffreichen oder sauerstoffarmen Bedingungen zu untersuchen Die Resultate deuten darauf hin dass die Cysteaminbehandlung die Strahlenschadigung vermindert und gleichzeitig zur Heilung der Schadigung beitragt

RÉSUMÉ

Les auteurs ont étudie l effet de la cysteamine sur les parametres de survie des cellules de hamster chinois irradiees avec et sans anoxie Les resultats font penser que le traitement par la cysteamine diminue la proportion de radiolesions et contribue en meme temps à la reparation de ces lesions

attributed to any particular protection of the recovery process by cysteamine treatment since the process cannot operate at all in the absence of an energy source. As an explanation consistent with the available data, a prolongation of the time period may be assumed during which the radiation injury remains recoverable in the cysteamine treated cells. Accordingly, the recovery process may function during the aerobic incubation period following the anoxic conditions, when the injury would be already fixed without cysteamine treatment. The data in Table 2 may be interpreted as indicating that much of the damage of the anoxically irradiated and cysteamine treated cells remains recoverable for one hour, but becomes fixed almost entirely at 2 hours. Aerobic conditions which would permit the function of the repair processes, are then no longer of any assistance. It is conceivable that fixation of the radiation damage may itself be an active, enzymatic process. The prolongation of the period of recovery may thus be due to an inhibition of the enzyme activity known to occur after cysteamine treatment (DE MARCO et coll. 1962, GOUTIER & BAUCNET MAHIEU 1969).

MAURO et coll. (1969) have also suggested that cysteamine may play an important role in permitting the function of repair processes in irradiated Chinese hamster and HeLa cells. They noted an increase of the extrapolation number and the split dose ratio due to cysteamine treatment. These authors, unlike the present writers, made their observations with aerobically irradiated cells. The difference in the present observations may be due to the fact that the cells used in the experiments of MAURO et coll. were in their logarithmic growth phase while the cells in the present experiments were derived from cultures in a plateau phase of growth. As described previously (HAHN 1968, REVESZ & LITTBRAND 1969) logarithmically growing cells have a greater capacity for recovery than cells in later growth phases. It is therefore conceivable that the more rapidly growing cell type is able to take better advantage of a period of recovery, prolonged by cysteamine, than the more slowly growing cells.

The effect of cysteamine on the recovery mechanism demonstrated by the present experiments and those of MAURO et coll. to which reference has been made supports the idea that the action of this compound may be related to a great extent to its interaction with physiologic protective mechanisms (REVESZ 1969).

Conclusions

Cysteamine treated Chinese hamster cells were exposed to different single doses of radiation under anoxic conditions. The D_0 value and the extrapolation number were increased by a factor of 2.4 and 1.6 respectively, in comparison to untreated cells. When exposures were made under oxic conditions the D_0

value increased by a factor of 1.1 but the extrapolation number failed to change significantly.

Exposure of cysteamine treated cells to split doses increased the survival by a factor of 1.5 in comparison to the survival after a single exposure to the same total dose when anoxic conditions prevailed during the irradiations. No similar increase in the survival of the untreated cells was noted. When oxic conditions were maintained during irradiations, exposure to split doses increased the survival of both the cysteamine treated and untreated cells by a factor of about 2 in comparison to a single exposure to the same total dose.

When the anoxic conditions during the exposures were maintained for 1 hour after irradiation and before the aerobic incubation of cells, the cysteamine induced increase of the split dose survival was lower than when aerobic conditions followed immediately. Only a slight increase of the split dose survival was noted when the anoxic conditions were maintained for 2 hours.

The data are consistent with the assumption that cysteamine prolongs the time period during which the radiation damage remains recoverable and before it is fixed irreversibly.

Acknowledgements

The authors wish to thank Mrs. Ingegerd Hedlöf and Miss Rut Jonsson for their technical assistance. The work was supported by grants from the Swedish Cancer Society, the Sir *Samuel Scott of Yews Trust* and the International Atomic Energy Agency.

SUMMARY

The effect of cysteamine on the survival parameters of oxically or *anoxically irradiated* Chinese hamster cells was investigated. The results suggest that cysteamine treatment decreases *the* production of radiation damage and at the same time contributes to repair of such damage.

ZUSAMMENFASSUNG

Zellgewebe des chinesischen Hamsters wurde benutzt, *um den Effekt des* Cysteamins auf die Überlebungsparameter nach Bestrahlung *unter sauerstoff*reichen oder sauerstoffarmen Bedingungen zu untersuchen. Die Resultate *deuten darauf* hin, dass die Cysteaminbehandlung die Strahlenschädigung vermindert und gleichzeitig zur *Heilung* der Schädigung beiträgt.

RÉSUMÉ

Les auteurs ont étudié l'effet de la cystéamine sur les paramètres de survie des *cellules de* hamster chinois irradiées avec *et sans* anoxie. Les résultats font penser que le *traitement par* la cystéamine diminue la *proportion de* radiolésions et contribue en même temps à la *ré*paration de ces lésions.

attributed to any particular protection of the recovery process by cysteamine treatment since the process cannot operate at all in the absence of an energy source. As an explanation consistent with the available data, a prolongation of the time period may be assumed during which the radiation injury remains recoverable in the cysteamine-treated cells. Accordingly, the recovery process may function during the aerobic incubation period following the anoxic conditions, when the injury would be already fixed without cysteamine treatment. The data in Table 2 may be interpreted as indicating that much of the damage of the anoxically irradiated and cysteamine treated cells remains recoverable for one hour, but becomes fixed almost entirely at 2 hours. Aerobic conditions which would permit the function of the repair processes, are then no longer of any assistance. It is conceivable that fixation of the radiation damage may in itself be an active, enzymatic process. The prolongation of the period of recovery may thus be due to an inhibition of the enzyme activity known to occur after cysteamine treatment (DE MARCO et coll. 1962, GOUTIER & BAUGNET-MAHIEU 1969).

MAURO et coll. (1969) have also suggested that cysteamine may play an important role in permitting the function of repair processes in irradiated Chinese hamster and HeLa cells. They noted an increase of the extrapolation number and the split dose ratio due to cysteamine treatment. These authors, unlike the present writers, made their observations with aerobically irradiated cells. The difference in the present observations may be due to the fact that the cells used in the experiments of MAURO et coll. were in their logarithmic growth phase while the cells in the present experiments were derived from cultures in a plateau phase of growth. As described previously (HAHN 1968, REVESZ & LITTBRAND 1969) logarithmically growing cells have a greater capacity for recovery than cells in later growth phases. It is therefore conceivable that the more rapidly growing cell type is able to take better advantage of a period of recovery, prolonged by cysteamine, than the more slowly growing cells.

The effect of cysteamine on the recovery mechanism demonstrated by the present experiments and those of MAURO et coll. to which reference has been made, supports the idea that the action of this compound may be related to a great extent to its interaction with physiologic protective mechanisms (REVESZ 1969).

Conclusions

Cysteamine treated Chinese hamster cells were exposed to different single doses of radiation under anoxic conditions. The D_0 value and the extrapolation number were increased by a factor of 2.4 and 1.6, respectively, in comparison to untreated cells. When exposures were made under oxic conditions, the D_0

FROM THE DEPARTMENT OF RADIOLOGY, YALE UNIVERSITY SCHOOL OF MEDICINE, NEW HAVEN, CONNECTICUT, USA

MATHEMATICAL SIMULATION OF RADIATION THERAPY OF SOLID TUMORS

II Fractionation

by

JAMES J FISCHER

The importance of dose fractionation in radiation therapy is generally well recognized (ELLIS 1968 FOWLER 1966 and THOMLINSON 1967) However despite extensive research in this field there still exists considerable uncertainty about the identity and relative importance of the basic underlying mechanisms responsible for the observed effects and thus there is difficulty in choosing the optimal fractionation regimen to obtain the maximum therapeutic advantage in any given clinical situation While there have been numerous attempts in the past to derive the observed time dose relationships from known radiobiologic principles (LAJTHA & OLIVER 1961 FOWLER & STERN 1963) these proved to be not totally satisfactory and the more recent tendency has been to look for empirical rules which will permit predictions of the effects of alterations of fractionation schedules (COHN 1968 COHEN & SCOTT 1968 and ELLIS 1969)

Despite past experience it seemed promising to study fractionation using a a recently developed mathematical model simulating the behavior of solid tumors during radiation therapy, which has as one of its advantages a provision for the re-oxygenation of initially hypoxic tumor cells during the treatment course

Submitted for publication 1 December 1969

REFERENCES

ASHBY R R and BONTE F J The metabolic requirements for repair of sublethal radiation damage Radiat Res 35 (1968), 512

BACQ Z M Chemical protection against ionizing radiation Charles C Thomas Springfield Illinois 1965

BRYANT P E Survival after fractionated doses of radiation Modification by anoxia of the response of Chlamydomonas Nature 219 (1968) 75

DE MARCO C MONDOVI B and CAVALLINI D Temporary supression of diamine oxidase (histaminase) activity by cysteamine Biochem Pharmacol 11 (1962) 509

EAGLE H Amino acid metabolism in mammalian cell cultures Science 130 (1959) 432

GOUTIER R and BAUGNET MATHIEU L Action of SH containing radioprotectors on nucleic acid metabolism *In* Radiation damage and sulphydryl compounds International Atomic Energy Agency Vienna 1969

HAHN G M Failure of Chinese hamster cells to repair sub lethal damage when X irradiated in the plateau phase of growth Nature 217 (1968) 741

HOWARD A The oxygen requirement for recovery in split-dose experiment with Oedogonium. Int J Radiat Biol 14 (1968), 341

KEMBER N F Hypoxia and recovery in growth of cartilage in vivo Int J Radiat Biol 13 (1967) 387

LITTBRAND B Survival characteristics of mammalian cell lines after single or multiple exposures to roentgen radiation under oxic or anoxic conditions Acta radiol Ther Phys Biol 9 (1970) 257

— and REVÉSZ L The effect of oxygen on cellular survival and recovery after radiation Brit J Radiol 42 (1969) 914

MAURO F GRASSO A and TOLMACH L J Cellular sulfhydryl groups and the response of cultured mammalian cells to X irradiation Biophys J 9 (1969), 1377

PHILLIPS T L Qualitative alteration in radiation injury under hypoxic conditions Radiology 91 (1968) 529

RÉVÉSZ L Interplay between natural and artificial radiation protection *In* Radiation damage and sulphydryl compounds International Atomic Energy Agency Vienna 1969

— and LITTBRAND B Fractionated irradiation and the effect of oxygen *In* Progress in Radiology Excerpta Medica Intern Congress Series No 105 p 1476 Amsterdam 1967

— — Culture age and cellular radiosensitivity Exp Cell Res 55 (1969) 283

— — Chemical protection of the recovery process *In* The Proceedings of the International Symposium on Biological Aspects of Radiation Protection Kyoto 1969

— — The composite radioprotective and radiosensitizing effect of an organic free radical *In* Radiation protection and sensitization p 217 Taylor & Francis London 1970

SINCLAIR W K Protection by cysteamine against lethal X ray damage during the cell cycle of Chinese hamster cells Radiat Res 39 (1969) 135

VERGROESEN A J BUDKE L and VOS O Protection against X irradiation by sulphydryl compounds II Studies on the relation between chemical structure and protective activity for tissue culture cells Int J Radiat Biol 13 (1967) 77

WOLFF S and LUIPPOLD H E Metabolism and chromosome break rejoining Science 122 (1955) 231

— — The biochemical aspects of chromosome rejoining Genetics 43 (1958) 493

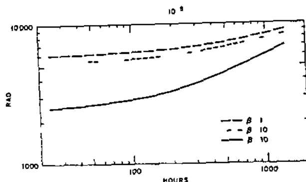


Fig 1 Calculated Strandqvist curves for a 95 per cent probability of tumor cure plotted on log dose log time scales for the model tumor with $\alpha=10^{5}$ i e no tumor cell division and $\beta=1$ 10^{10} and 10^{20} corresponding respectively to initial cell populations totally hypoxic 10 per cent hypoxic and totally oxygenated

obtained by others Examination of the cell survival curves obtained from eq (1) upon substitution of these values reveals that for very low radiation doses less than 150 rad a greater fraction of the hypoxic cells than of the oxygenated cells is killed This effect is due of course to the larger shoulder in the curve for the oxygenated cells and while such low dose rates will not be considered here, it is interesting to note that in this unusual situation a re-oxygenation mechanism would increase the dose required for tumor cure

The computer program previously described can be modified to produce complete Strandqvist curves directly The radiation dose plotted for each total time will produce a cure probability between 95 and 96 per cent The time period actually recorded extends to the next calculation time following the final dose necessary to reach this cure probability thus the single treatment point would appear at a value of 24 hours on the abscissa The loci of time and dose values necessary to produce the iso-effect 95 to 96 per cent cure probability are plotted on a log log graph in the traditional manner suggested by Strandqvist and widely used by others Unless otherwise stated a five day Monday through Friday treatment week is used

Results and Discussion

Strandqvist curves have been presented by others for a variety of tumor and normal tissue responses based on clinical data retrospectively examined and on experimental results from both laboratory and clinical sources (a number of

(FISCHER 1971) In fact, one of the most interesting immediate results was the prediction under certain conditions of anomalous behavior of the Strandqvist type time dose curves, which need not necessarily be monotonicly increasing, but can have a local relative minimum — A curve is said to be monotonicly increasing when its slope is always upward, i e is positive at all values of the abscissa A local minimum exists if the curve decreases and then increases again, the lowest point reached being called the minimum — The existence of such a minimum for human tumors would be of obvious importance in choosing an optimum fractionation regimen In order better to understand the conditions which lead to this result, Strandqvist curves have been calculated for a wide range of values of the parameters characterizing model tumors

Methodology A complete description of the model and the associated computer program has been given in the first paper in this series (FISCHER 1971) and only the important features will now be reviewed A solid tumor is considered to be composed of two types of cells, well oxygenated and hypoxic, and each type is killed according to the usual multi target, single hit relationship

$$S = 1 - (1 - e^{-D/D_0})^n \tag{1}$$

where S is the fraction of cells surviving, and where the values for n, the hit or extrapolation number, and D_o, the characteristic dose, depend on the degree of oxygenation

The cells which are killed by radiation, i e are no longer clonogenic, still exist until they attempt division, at which time they disintegrate All well oxygenated cells attempt reproduction with a rate constant a, in units of hr^{-1}, the living cells successfully double and the dead cells cease to exist Anoxic cells do not attempt to divide

The proportion of cells which are oxygenated is given by

$$\frac{N_{0r}}{N} = e^{-BN} \tag{2}$$

where N is the total number of cells living or dead, oxygenated or hypoxic It is evident from this relationship that re oxygenation will occur only when N decreases, which in turn will occur only if the rate constant a is reasonably large

The model tumor is characterized by the following parameters which unless otherwise indicated are used throughout this work *NO* the extrapolation number for the oxygenated cells, 4, *N 1* the extrapolation number for the hypoxic cells, 1 5, *DO*, the characteristic dose for the oxygenated cells, 100 rad *D 1* the characteristic dose for the anoxic cells, 250 rad, and γ, the division delay constant, 0 005 hours/rad

These values are consistent with experimental results for mammalian cells

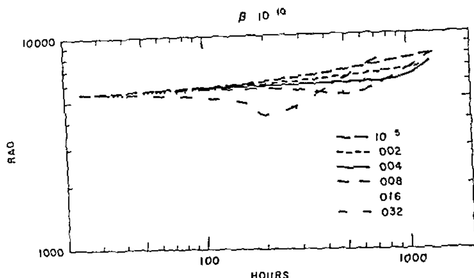


Fig 3 Calculated Strandqvist curves for the model tumor initially composed of 10 per cent hypo ic cells ($\beta=10^{10}$) for variou values of a 10^{5} to 0 032 The relative minima are clearly demonstrated

proportion of oxygenated cells in the tumor — One may speculate about the extent to which the fact that Strandqvist lines for normal tissue reaction are often steeper than those for tumor responses is based on the finding that normal tissues are more likely than tumors to be well oxygenated and well oxygenated cells are more likely than hypoxic cells to have higher extrapolation numbers — There is no general assurance that these lines will be straight However they must be either constant which will occur only if all pertinent extrapolation numbers are unity or they must be monotonicly increasing

The second mechanism responsible for the time dependence of the Strandqvist curves is the multiplication of the tumor cells In order to demonstrate this effect isolated from the influence of re oxygenating such curves were calculated for a variety of growth rates a with $\beta = 10^{0}$ a value which makes all cells initially oxygenated The results are presented in Fig 2 The values of a 0 032, 0 004 and 10 correspond respectively to doubling times of less than one day, one week and many years i e no growth Once again the net effect of this mecha ni m must always be to produce a monotonic increase in the Strandqvist lines

The third mechanism, re-oxygenation is more complex than the first two It was appreciated some time ago by THOMLINSON and others that initially hypoxic tumor cells might become better oxygenated and thus more radiosensitive

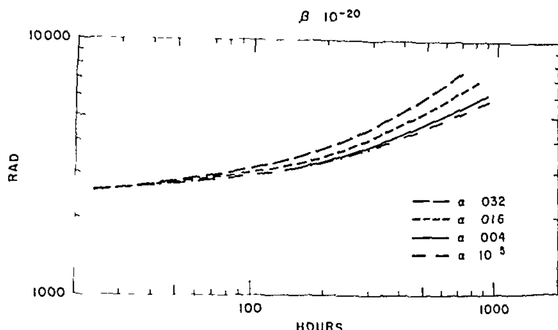


Fig 2 Calculated Strandqvist curves for the model tumor with $\beta = 10^{-20}$ i.e. all cells oxygenated with varying cell division rates $\alpha = 0.032$, 0.016, 0.004 and 10^{-5} corresponding to doubling times of approximately 20 hours, 10 hours, one week and years respectively

these have been collected by FOWLER & STERN 1963) Generally, these curves are linear on a log log scale over the range of dose rates commonly used in radiation therapy, with longer time periods requiring higher doses Considerable attention has been focused on the slopes of these straight lines in attempting to choose optimal treatment schedules At least three different mechanisms are thought to contribute to this time dependence of the required radiation dose The first of these results from the existence of the shoulder in the individual cell survival curves described by eq (1) and the possibility of Elkind type recovery, assumed in the model to be complete between each dose

The quantity $D_q = D$ ln n introduced by ALPER et coll (1962), corresponds to the radiation dose which is essentially wasted at each treatment because of the existence of the shoulder Clearly, a larger number of treatments will require a greater total dose to achieve any desired effect as a result of this mechanism This is illustrated in Fig 1, in which the cell multiplication rate constant $\alpha = 10^{-5}$ is chosen so that tumor growth and thus also re oxygenation are insignificant The Strandqvist curves for a range of β values are shown, each curve representing a tumor with a different initial proportion of hypoxic cells For the tumor parameters previously chosen, D_q is much larger for the oxygenated cells and thus the slope of the Strandqvist curves is directly related to the initial

Table 1

Total dose and total number of treatments (in parantheses) to achieve 95 per cent probability of cure for the indicated daily dose five treatments per week and growth constant α for a tumor characterized by $N = 10$ $\beta = 10^{10}$ $\gamma = 0\ 005$ $NO = 4$ $N1 = 1\ 5$ $DO = 100$ $D1 = 250$

Alpha	Daily dose				
	200	300	400	500	600
10	8 200 (41)	7 500 (25)	7 200 (18)	7 000 (14)	6 600 (11)
0 002	7 000 (35)	6 600 (22)	6 400 (16)	6 500 (13)	6 600 (11)
0 004	7 000 (35)	6 000 (20)	6 000 (15)	6 000 (12)	6 000 (10)
0 008	8 600 (43)	5 400 (18)	5 600 (14)	5 500 (11)	6 000 (10)
0 016		6 300 (21)	4 800 (1[illegible])	5 000 (10)	4 800 (8)
0 032		10 200 (34)	5 600 (14)	4 500 (9)	4 800 (8)

indication for split course therapy) On the other hand if α is too large the tumor will simply outgrow the treatments and will not be cured by any reasonable fractionated regimen These findings are illustrated in Fig 3 which shows the effects of varying α for a fixed $\beta = 10^{10}$

If β is too small the original proportion of hypoxic cells will be insignificant and re oxygenation will necessarily have little effect If it is too large there will be little cell division because of the hypoxia and re oxygenation will take place too slowly much as in the case for a very small α The effect of variation in β for $\alpha = 0\ 016$ is shown in Fig 4 The local minimum is clearly seen for values of α and β which seem realistic $\beta = 10^{10}$ which gives 10 per cent hypoxic cells initially and $\alpha = 0\ 016$ and 0 032 which give intrinsic doubling times of approximately one to three days

The effect of variations in the growth rate α shown in Fig 3 is somewhat unusual At the higher dose rates corresponding to the local minima the more rapidly growing tumors are cured with lower doses For more prolonged frac tionation however the Strandqvist lines begin to cross and the rapidly growing tumors require higher doses In fact there are particular combinations of α and daily dose rates which correspond to low total dose requirements for cure This is clearly illustrated in Table 1 where the dose for cure is recorded for different values of α for particular daily dose rates As an example the tumor with $\alpha = 0\ 002$ has such a low total dose for a daily dose of 400 rad

It is a not uncommonly held belief among physicians that rapidly growing poorly differentiated tumors are more radiosensitive and more easily cured locally than are more slowly growing tumors The origins of this impression which is based perhaps on the clinical observation of dramatic decreases in the

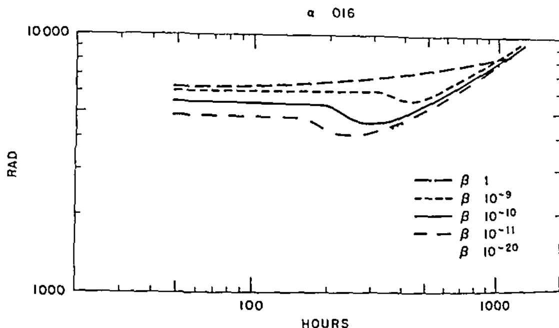


Fig 4 Calculated Strandqvist curves for the model tumor with intermediate cell division rate $\alpha = 0\ 016$ *(Doubling time 40 hours if all cells are actively dividing)* The initial proportion of hypoxic cells varies from 100 per cent ($\beta = 1$) to 0 per cent or ($\beta = 10^{-20}$)

during the course of fractionated radiation and that such a process would have profound effects in tumor therapy Such re oxygenation in solid tumors has now been demonstrated by several investigators (CHESHIRE & LINDOP 1969, HAWKES et coll 1968, HOWES 1969, and VAN PUTTEN & KALLMAN 1968) Typically, in these experiments a smaller total dose is needed to produce a given effect when given in two fractions rather than one

Whether this sensitization by re oxygenation will be sufficient in the case of a complex tumor treated with multiple fractions to overcome the effects of the survival curve shoulder and of cell reproduction, so that a negative slope of the Strandqvist line will actually be observed, will depend in a complex way on the various parameters of the system That such a condition can actually exist within the framework of this model is explicitly demonstrated in Fig 3 For example, the values $\alpha = 0\ 016$ $\beta = 10^{-10}$ lead to a Strandqvist line which shows a relative minimum at an overall treatment time of approximately 300 hours which is 1 000 rad below the single treatment dose In order for such a minimum to exist, both α and β must have values within certain limits, and in fact the limits for either will depend on the value chosen for the other If α is too small the cells killed by *radiation* will not attempt to reproduce sufficiently rapidly for significant re oxygenation to occur during the treatment period (This would be a possible

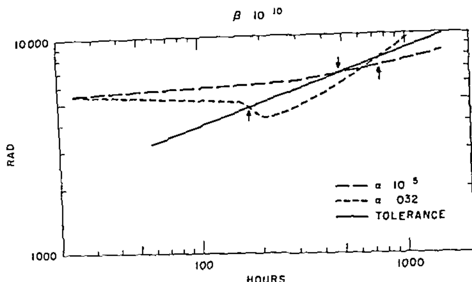


Fig 5 Calculated Strandqvist curves for slowly growing $\alpha = 10$ and rapidly growing $\alpha = 0\ 03^{?}$ model tumors compared with a normal tissue tolerance line of slope 0 33 and arbitrary position

The existence of such local minima in the Strandqvist curves will be of considerable importance in the design of an optimal fractionation scheme In Fig 5 a Strandqvist curve for normal tissue tolerance has been superimposed on two of the tumor response curves, one for rapid growth $\alpha = 0\ 032$ which shows such a minimum, and one for slow growth $\alpha = 10$ which is monotonicly increasing This tolerance line might represent an acceptable frequency of occurrence of some particularly important complication which in practice would limit the radiation dose Its lope is 0 33 consistent with the well known ELLIS tables and other published data and greater than that of the slowly growing tumor The actual location of the line was chosen arbitrarily to be most illustrative

The slowly growing tumor can be treated sati factorily in any total time greater than that at the intersection of the tumor control and tolerance lines indicated by the downward arrow A dose must be chosen to give a time dose point below the tolerance line and above the control line A better result should be possible in terms of less chance of complication and higher cure probability, the longer the time chosen No clear optimum is indicated the maximum time used being limited only by practical logistic considerations and by the fact that these lines must eventually cease to apply for very prolonged treatment courses Such a

Table 2

Tumor mass regression rates and curative doses for the model tumor with $\beta = 10^{-10}$ variable α treated with 300 rad daily until a 95 per cent chance of cure is reached

(1) Model tumor with α =	(2) Total dose (treatment number) reached when $N = 5 \times 10^{8}$	(3) $N = 10^{8}$	(4) Dose (treatment number) for 95 % cure	(5) Value of N on day of last treatment for 95 % cure
10^{-5}	—	—	7 500 (25)	0.993 × 10^{8}
0.002	3 900 (13)	—	6 600 (22)	0.28 × 10^{8}
0.004	2 100 (7)	6 000 (20)	6 000 (20)	0.89 × 10
0.008	1 500 (5)	3 000 (10)	5 400 (18)	0.15 × 10
0.016	900 (3)	1 800 (6)	6 300 (21)	0.39 × 10
0.032	900 (3)	1 500 (5)	10 200 (34)	0.44

size of such tumors under treatment and on some familiarity with the now 60 year-old law of Bergonie and Tribondeau', and the necessity for a more precise understanding of the concept of radiosensitivity have been elegantly espoused by ANDREWS, and others. The rate of decrease in size of a bulk lesion cannot generally be directly correlated with the eventual cure. Such a result has been observed both clinically and experimentally (SUIT 1965) and is predicted by this model and illustrated explicitly in Table 2 for the tumor with $\beta = 10^{-10}$, variable α, treated with daily doses of 300 rad. The dose level reached when the tumor volume is reduced to one half, $N = 5 \times 10^{8}$ cells, column (2), and one tenth, $N = 10^{8}$ cells, column (3), is presented as well as the value of N at the time of the final treatment needed for cure, column (5). The regression rate depends only on α but not upon the curative dose, column (4), which for this deliberately chosen dose rate is a minimum for $\alpha = 0.008$ and larger for both slower and faster growth rates. The pitfall in confusing rate of response and long term cure is obvious.

Despite these qualifications, the importance for re-oxygenation of rapid growth and the resulting rapid regression, which has been clearly demonstrated in Fig. 3 and Table 1, must not be underestimated. The lowest curative dose seen in Fig. 3 is indeed for the tumor of a largest α. The resolution of this seeming paradox is simply stated: while α and the resulting rate of decrease in size of a tumor treated at a given daily dose rate does not correlate with the cure probability for any total dose, a large α does permit the selection of a dose rate which will cure the tumor with a lower total dose than possible for any smaller α.

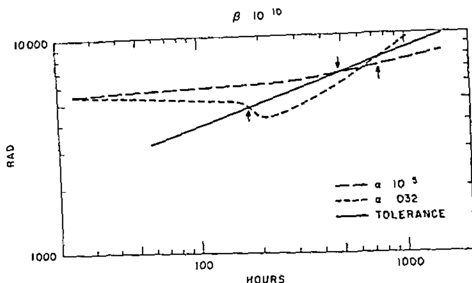


Fig 5 Calculated Strandqvist curves for slowly growing $\alpha = 10^{5}$ and rapidly growing $\alpha = 0.032$ model tumors compared with a normal tissue tolerance line of slope 0 33 and arbitrary position

The existence of such local minima in the Strandqvist curves will be of considerable importance in the design of an optimal fractionation cheme In Fig 5 a Strandqvist curve for normal tissue tolerance has been superimposed on two of the tumor response curves one for rapid growth $\alpha = 0.032$ which shows such a minimum and one for slow growth $\alpha = 10$ which is monotonicly increasing This tolerance line might represent an acceptable frequency of occurrence of some particularly important complication which in practice would limit the radiation dose Its slope is 0 33 consistent with the well known Ellis tables and other published data and greater than that of the slowly growing tumor The actual location of the line was chosen arbitrarily to be most illustrative

The slowly growing tumor can be treated satisfactorily in any total time greater than that at the intersection of the tumor control and tolerance lines indicated by the downward arrow A dose must be chosen to give a time dose point below the tolerance line and above the control line A better result should be possible in terms of less chance of complication and higher cure probability the longer the time chosen No clear optimum is indicated the maximum time used being limited only by practical logistic considerations and by the fact that these lines must eventually cease to apply for very prolonged treatment courses Such a

situation has been described for skin tumors (VON ESSEN 1963) based on clinical and experimental data

For the rapidly growing, potentially re oxygenated tumor, the situation is quite different The desired results can be obtained only within the time limits specified by the intersections at the upward arrows Furthermore, barring some unexpected irregularity in the dose response curve for the complication, at least one relative optimum time dose point will exist, where the separation between the two curves is a maximum Clearly this combination of dose and time should be used in this particular clinical situation

One might wonder why Strandqvist curves showing these distinct minima have not been observed if in fact this model is realistic, and several reasons come to mind Much of the published data is based on retrospective examination of time dose combinations used in the past with some rough estimate of their effectiveness As such it may simply be too crude and too influenced by uncontrolled selection factors to reveal such a shape

Often the measured end point for tumor response is not long term local cure but disappearance of a mass lesion either measured directly or indicated by relief of symptoms From the detailed earlier discussion of factors influencing tumor regression rates, it should be obvious that such end points will not necessarily correlate with cure probability or demonstrate the local minima in Strandqvist curves

The most reliable fractionation data seems to be that for skin tumors which usually show straight Strandqvist curves However, these tumors are often slowly growing, usually small when treated, and probably well oxygenated, all factors previously shown to favor such monotonicly increasing curves

Recently, an attempt has been made (HOWES & FIELD 1968) to re examine the widely quoted time dose data of FRIEDMAN & PEARLMAN (1955) in light of the possibility that re oxygenation might have been taking place during treatment It would seem that their data is insufficient to definitely establish this point, but certainly it is suggested

If local minima do exist in the Strandqvist curves for cure of rapidly growing partially hypoxic tumors, as suggested by this model, they will be of obvious clinical importance, and attempts to identify them should be made both in appropriate laboratory tumor systems and in clinical situations

Acknowledgements

I would like to thank D B Fischer for carrying out the necessary computer programming M M Kligerman and H S Reinhold for valuable suggestions for improvement and Julia Chang and Margaret C Jost for accumulating and plotting the calculated data This work was supported by United States Public Health Service grant No CA 06519

SUMMARY

A recently developed mathematical simulation of the behavior of solid tumors during radiation therapy has been applied to the problem of dose fractionation One of the advantages of this particular model is that it contains a provision for the reoxygenation of initially hypoxic tumor cells Because of this feature it predicts under certain circumstances *that the calculated Strandqvist lines* for tumor cure need not be straight or even monotonicly increasing but indeed may have local relative minima The particular characteristics of the tumor and the fractionation regimen which lead to this finding are determined and discussed in detail

ZUSAMMENFASSUNG

Eine kurzlich entwickelte mathematische Simulation des Verhaltens solider Tumoren wahrend einer Strahlentherapie ist auf das Problem der Dosis Fraktionierung angewendet worden Eines der Vorteile dieses speziellen Modells ist dass es die Reoxygenierung von *initial hypoxischen Tumor Zellen* berucksichtigt *Aufgrund* dieser Eigenschaft sagt es unter bestimmten Umstanden voraus dass die berechneten Strandqvist Linien zur Tumorheilung nicht geradlinig oder auch gleichformig ansteigend zu sein brauchen sondern vielmehr lokal relative Minima haben konnen Die besondern Charakteristika des Tumors und des Fraktionierungsregims die zu diesem Befund fuhren sind bestimmt und werden im einzelnen besprochen

RÉSUMÉ

Une simulation mathematique du comportement des tumeurs solides au cours du traitement par les radiations *recemment mise au point a ete appliquee au probleme du fractionnement* de la dose Un des avantages de ce modele particulier est qu il comporte la possibilite de tenir compte de la reoxygenation de cellules tumorales initialement hypoxiques En raison de ce caractere ce modele prevoit que dans certaines circonstances les lignes de Strandqvist calculees pour le traitement de la tumeur ne sont pas necessairement droites ni meme regulierement croissantes mais peuvent avoir en realite des minimums locaux relatifs La caracteristique particulière de la tumeur et le type de fractionnement qui conduisent a ce resultat sont determinees et discutées en detail

REFERENCES

ALPER T FOWLER J F MORGAN R L et coll The characterization of the type C survival curve Brit J Radiol 35 (1962) 722

ANDREWS J R The radiobiology of human cancer radiotherapy W B Saunders Philadelphia 1968

CHESHIRE P J and LINDON P J The influence of intracellular recovery and hypoxic cells on the radiation response of mammary tumours and skin in C_3H mice Brit J Radiol 42 (1969) 215

COHEN L Theoretical "iso survival" formulae for fractionated radiation therapy Brit J Radiol 41 (1968), 522

— and SCOTT M J Fractionation procedure in radiation therapy a computerized approach to evaluation Brit J Radiol 41 (1968), 529

ELLIS F The relationship of biological effect to dose time fractionation factors in radiotherapy *In* *Current topics in radiation research* 4 (1968)

VON ESSEN C F A spatial model of time-dose area relationships in radiation therapy Radiology 81 (1963) 881

FISCHER J J A mathematical simulation of radiation therapy of solid tumors Calculations. Acta radiol Ther Phys Biol 10 (1971) 73

FOWLER J F Radiation biology as applied to radiotherapy *In* Current topics in radiation research Edited by M Ebert and A Howard North Holland Publishing Company Amsterdam 1966

— and STERN B E Dose time relationships in radiotherapy and the validity of cell survival curve models II Brit J Radiol 36 (1963) 163

FRIEDMAN M and PEARLMAN A W Time dose relationship in irradiation of recurrent cancer of the breast Amer J Roentgenol 73 (1955) 986

HAWKES M J HILL R P LINDOP P J et coll The response of C_3H mammary tumours to irradiation in single and fractionated doses Brit J Radiol 41 (1968) 134

HOWES A E An estimation of changes in the proportions and absolute numbers of hypoxic cells after irradiation of transplanted C_3H mouse mammary tumours Brit J Radiol 42 (1969) 441

— and FIELD S B The oxygen effect a new look at Friedman and Pearlman Brit J Radiol 41 (1968) 554

LAJTHA L G and OLIVER R Some radiobiological considerations in radiotherapy Brit J Radiol 34 (1961) 252

SUIT H Prognostic significance of extent of tumour regression at completion of radiation therapy Radiology 84 (1965) 1100

THOMLINSON R H *In* Modern trends in radiotherapy Edited by T J Deeley and C A P Wood Butterworths London 1967

VAN PUTTEN L M and KALLMAN R F Oxygenation status of a transplantable tumor during fractioned radiation therapy J nat Cancer Inst 40 (1968) 441

FROM THE ONTARIO CANCER FOUNDATION, LONDON CLINIC, LONDON, ONTARIO, CANADA

LiF SURFACE AND DEPTH DOSE MEASUREMENTS OF MEGAVOLTAGE PHOTON AND ELECTRON BEAMS

by

M. KARTHA and J. C. F. MACDONALD

Using megavoltage photon beams the measurement of absorbed dose at the position of a deep seated tumor may be achieved by several techniques. Dose determination at the skin and in the subcutaneous region where the dose is changing rapidly is more difficult. When high energy electron beams are used a determination of absorption pattern in and close to an heterogeneity in the absorber especially when it is very small becomes difficult unless a very small dosemeter is available. Extrapolation chambers have been successfully employed for absorbed dose measurements in the build up regions but they are instruments difficult to construct and tedious to use. The use of ionization chambers for measurement in the build up region and even at the peak dose depth is shown to be undesirable due to the errors involved in positioning and lack of electronic equilibrium (HOSPITAL PHYSICISTS ASSOCIATION 1969).

In this article the use of LiF thermoluminescent powder (TLD 100) in thin layers (approximately 20 μm) for the measurement of absorbed dose in the

Part of this paper was presented at the Second International Conference on Medical Physics, Boston, Massachusetts, 11 to 15 August 1969. The work was partly supported by a grant from the Ontario Cancer Treatment and Research Foundation. M. K. is now at The Radiation Therapy Division, The Ohio State University, College of Medicine, Columbus, Ohio, U.S.A. Submitted for publication 23 February 1970.

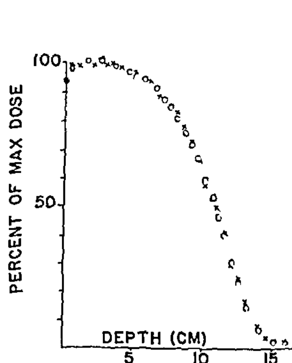


Fig 1

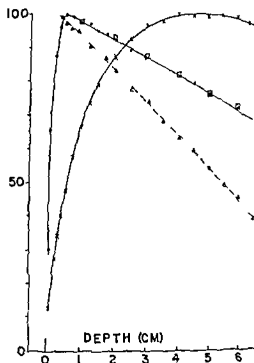


Fig 2

Fig 1 Results of measurements using a single irradiation of 25 stacked monocrystalline TL dosemeters (o) and multiple irradiations of single dosemeters (×) at different depths 30 MeV electrons 8 cm circular plastic applicator

Fig 2 Build up curves measured with monocrystalline TL layer dosemeters Field size 4×4 cm △ 250 kV roentgen rays × 32 MV roentgen rays ● ^{60}Co measured □ ^{60}Co according to British Journal of Radiology Supplement 10

region of high dose gradient is reported It has been employed to measure relative doses at the surface and in the build up region of 250 kV roentgen rays, ^{60}Co radiation and 32 MV roentgen rays The depth dose curves of 10 to 35 MeV electron beams in both homogeneous and heterogeneous absorbers have also been similarly measured

Thermoluminescent dosimetry (TLD) has gained popularity in clinical dose measurement because of its approximate tissue equivalence, reproducibility, commercial availability and its ability to store the absorbed energy for long periods (CAMERON et coll 1964) Its dosimetric response has been found to be linear to approximately 1 000 rad for roentgen and gamma rays (CAMERON et coll 1964) and to 5 000 rad for high energy electrons (KARZMARK et coll 1964 KARTHA 1969) Also its response to high energy electrons and photons with LET less than that of ^{137}Cs has been shown to be constant (WORTON & HOLLOWAY 1966, PINKERTON et coll 1966, KARTHA 1969, SUNTHARALINGAM & CAMERON

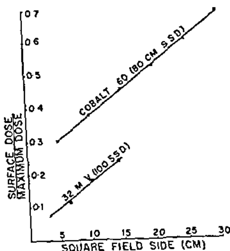


Fig 3 Relative surface dose at the center of square ⁽Co and 32 MV roentgen ray fields as a function of field size

1969 BINKS 1969) Because the energy spectrum and the dose level vary with depth in the absorber especially for electron beams the ideal system for the measurement of depth dose must have a linear dose response which is independent of energy Because LiF fulfills these requirements it has been extensively used in the form of encapsulated dosemeters for depth measurement of electron and photon beams (ALMOND et coll 1967, HENDEE 1966, HENDEE et coll 1968) Since the TLD 100 phosphor is in the form of crystals of approximately 100 mesh Tyler its use can provide excellent spatial resolution which is of primary interest in the measurement of dose in a high gradient region (ROBINSON & MCDOUGALL 1966) The large dimension of TLD 100 in capsule form does not provide enough accuracy in the measurement of such doses The LiF phosphor has been used in techniques similar to that used in this work for the measurement of ^{90}Sr beta depth dose (McDONALD 1965) and cellular radiation dose (HENDEE et coll 1967)

Materials and Method The TLD 100 phosphor used in the measurement was spread evenly into a polystyrene disc of 1 mm thickness to fill a small recess of 0 2 mm depth and 10 mm diameter This could hold approximately 35 mg LiF phosphor with the powder surface exposed By stacking these discs in a closely fitting hole in a polystyrene phantom which is considered tissue equivalent (SCRAD 1966) it was possible to measure the dose at 1 mm intervals of depth from the surface through the build up regions to any desired depth up to 20 cm Since the dosimetric phosphor is exposed at the surface without any overlying material, the surface dose measurement is most accurate

Using this technique, a complete depth dose curve could be obtained with a single radiation exposure However the introduction of LiF phosphor in the tissue equivalent phantom may result in a differential absorption, especially in the electron beam measurements In order to examine this possibility, the result of measurements with a single stack irradiation was compared with those obtained with multiple irradiations of single monocrystalline layer dosemeters A typical curve comparing the two sets of results is shown in Fig 1, which indicates agreement within experimental limits

The 1 mm build up of heavily filtered 250 kV roentgen rays (2 6 mm Cu HVT) was measured by this technique to demonstrate its usefulness The depth dose curves for this roentgen ray beam are shown in Fig 2, along with similarly measured curves for ^{60}Co and a 32 MV photon beam The surface doses are 98, 30 and 10 % respectively of the peak dose, which occurs at depths of 1 mm, 4 mm and 40 mm On the ^{60}Co curve the standard depth dose data (Brit J Radiol Supplement 10) are superimposed for comparison

The radiation sources employed in this work were a 250 kV Westinghouse therapy unit, a Theratron 80 Cobalt 60 teletherapy unit, and a Brown Boveri Asklepitron 35 medical betatron The betatron was adjusted to put out a 32 MV roentgen ray beam and electron beams in the energy range from 10 to 35 MeV The roentgen ray beam is defined by a continuously variable diaphragm assembly, while electron beam definition is achieved at the skin by a variable collimator, or one of a set of fixed plastic applicators, or brass cutouts placed at the surface of the absorber

Thermoluminescent measurements were made using a Madison Research Model S 2 thermoluminescent radiation exposure meter The reproducibility of dose measurements with this instrument was within ± 1 % in the dose range 50 to 5 000 rad (KARTHA 1969, WORTON & HOLLOWAY 1966) The large number of measurements required was, however, tedious and timeconsuming since each reading cycle requires at least one minute of undivided attention Consequently, an automated TLD reading device was designed and constructed in order to simplify the measurement procedure (KARTHA & MACDONALD 1969) This device makes possible the unattended measurement of 24 samples sequentially, the resulting data being stored in an electronic memory circuit and typed out when required

Surface dose

The relative surface dose at the center of square ^{60}Co and 32 MV roentgen ray fields as determined by this method, are plotted in Fig 3 against the length of the field side and is approximately linear in both cases These findings are in

Table

Surface doses as a percentage of the dose maximum illustrating the effect of beam size and method of collimation

Accelerated electron energy (MeV)	Plastic applicator		Variable collimator		No collimation Open field
	4 cm diameter	14×12 cm	4×4 cm	14×12 cm	
10	95	88	92	88	84
15	94	92	92	93	84
20	93	93	93	94	86
25	94	92	93	94	88
30	92	92	94	92	90
35	91	92	93	93	89

agreement with those of SMITH et coll (1958) and indicate that the increase in central dose is caused by scatter from the diaphragm system

The per cent surface doses for electron beams of various sizes and *methods of* collimation in the energy range 10 to 35 MeV, are listed in the Table In contrast to the situation described above the central surface dose for collimated electron beams is found to *decrease slightly* with increasing size In this case the beam limiting diaphragms are in contact with the skin surface and as the field size increases electrons scattered from them are less likely to contribute to the dose at the field *center* When the collimators are removed the resulting reduction in central surface dose indicates the magnitude of this scatter contribution as illustrated in Fig 4 where the results of collimation by a 12 × 14 cm plastic applicator are compared to collimation by a thick brass cutout placed on the surface The difference in the area under the curves represents the scatter contribution from the plastic applicator which is more significant at low energies and when small plastic applicators are used *In addition* when the cutouts are used at the surface of the absorber to define the electron beam the dose distribution along the plane of the field is *more uniform* Consequently the use of such brass cutouts results in lower skin dose and a more uniform dose distribution over the field area which is especially advantageous for most therapeutic set ups

Electron beam dosimetry

Homogeneous absorbers The dose gradients encountered in the therapeutic use of high energy electron beams are easily measured with the monocrystalline layer technique Examples of central axis dose curves are given in Figs 4 5 and 6

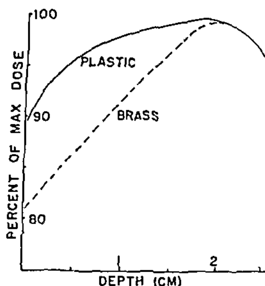


Fig 4 10 MeV electrons 14×12 cm field size Depth dose curves for the region between the surface and the maximum when (1) an extended plastic applicator and (2) a cutout in a thick brass plate is used to define the beam

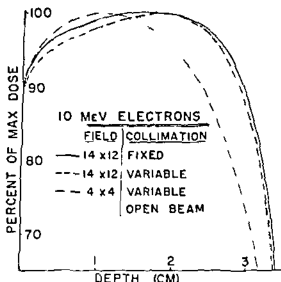


Fig 5

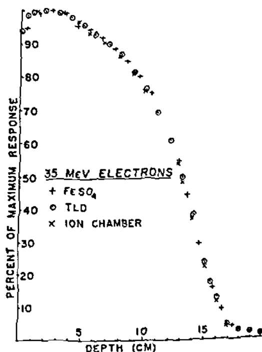


Fig 6

Fig 5 *Comparison* of central axis depth dose curves for 10 MeV electrons illustrating the effect of field size and method of collimation

Fig 6 Depth dose curve for 35 MeV electrons as measured with three dosimetric systems

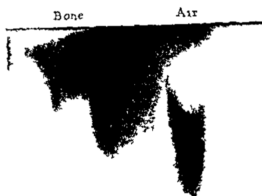


Fig 7 Film dosimetric measurement of a 35 MeV 14×10 cm electron beam absorption in a tissue equivalent rubber phantom (TEMEX) containing bone and air for inhomogeneity

It is seen from Fig 5 that for a 10 MeV beam the shape of the depth dose curve depends upon the field size and type of collimator This is found to be true at all energies up to 35 MeV and shows the undesirability of therapeutic electron beams of small cross section

An intercomparison of central axis depth dose curves for an 8 cm diameter 35 MeV electron beam as measured with the ferrous sulphate mini dosemeters (KARTHA 1970) a Baldwin Farmer ionization chamber and LiF monocrystalline layer dosemeters is shown in Fig 6 The ionization chamber measurements have been corrected to the effective center (DUTREIX & DUTREIX 1966) The agreement demonstrates the usefulness of the monocrystalline layer TLD technique for such measurements

Heterogeneous absorbers The TLD technique described in the preceding was also used to measure the absorption curve of electron beams in the heterogeneous phantoms The preferential absorption of electrons in higher electron density materials have been well established (LAUGHLIN et coll 1965) This is further illustrated in Fig 7 where the absorption pattern of a 35 MeV electron beam in a heterogeneous absorber is given The heterogeneity was produced by introducing bone and air cavities in a tissue equivalent (TEMEX) phantom A Kodak type M film sandwiched in the phantom was irradiated at 3° to the beam axis The regions of protection in and beyond the inhomogeneity indicate that the absorption in bone is greater than in soft tissue producing a low dose protection

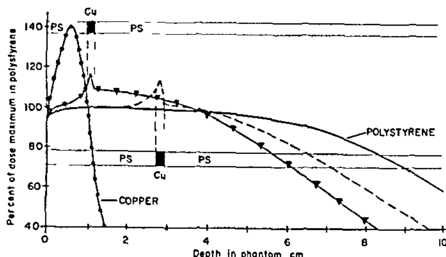


Fig 8 The effect of the presence of high electron density absorber (copper) in a tissue equivalent (polystyrene) phantom measured with monocrystalline layer TLD 100 The depth dose curves for homogeneous copper and polystyrene phantoms are also inserted

beyond it On the other hand, the opposite situation prevails where air is present In order to study these effects in further detail depth dose curves in heterogeneous absorbers, produced by the introduction of cork, bone, plaster of Paris, magnesium, aluminium, copper or lead into a polystyrene phantom, were measured with the monocrystalline TLD 100 layers These curves showed an increased absorption in and around the higher electron density material, and a considerable decrease in the average range of the electron beam A typical set of curves is shown in Fig 8 An 8 cm diameter 30 MeV electron beam was used and the TLD 100 was spread in thin layers between the 0 5 mm copper sheets introduced in the polystyrene phantom The depth dose curve for the same electron beam in a homogeneous copper and polystyrene phantom, measured by the same method is also given along with these curves Introduction of the 2 mm copper perturbed the energy dissipation pattern considerably, which seemed to be strongly dependent upon the position of the inhomogeneity in the absorber Except for the extent and amplitude of the peak at the position of inhomogeneity in the absorber, the results were identical when other materials were used in place of copper

Discussion

The value of LiF TLD has been increased by its extension to dose measurements using very thin layers of approximately 20 μm The feasibility of making measurements at the surface and at separations of a millimeter or less has been demonstrated It allows the measurement of a complete depth dose curve in

homogeneous as well as heterogeneous absorbers using single exposure Considering the excellent reproducibility and electron energy independence, the TLD 100 when calibrated provides accurate means of measurement of depth dose curves Since the high energy electron beams loses energy fairly uniformly at a rate of approximately 2 25 MeV per cm of water (or tissue equivalent absorber), a dosimeteric system whose response is independent of beam energy is extremely useful Furthermore in clinical dosimetry a point dosemeter is highly desirable because the absorbers involved in radiation therapy are invariably heterogeneous and the determination of absorption at a point becomes very important The use of monocrystalline layers of TLD 100 made possible the determination of surface dose and demonstrated the advantages of using beam defining cutouts in electron beam therapy over the conventional electron beam cones The results of the depth dose measurements in heterogeneous phantoms illustrate the superiority of this technique over other dosimetric methods Additional information has been obtained especially in regions of high dose gradient

SUMMARY

A simple dosimetric method using LiF TLD 100 phosphor in monocrystalline layers is presented This technique is shown to be especially useful in the measurement of surface dose absorbed dose in the region below the surface and electron depth dose in both homogeneous and heterogeneous absorbers The measurement of a complete depth dose curve including the surface dose and the dose in regions of sharp gradients is made possible by using stacks of the monocrystalline layers of TLD 100

ZUSAMMENFASSUNG

Eine einfache dosimetrische Methode bei der LiF TLD 100 Phosphor in monokristallinischen Schichten verwendet wird ist dargestellt Es wird gezeigt dass diese Technik besonders anwendbar bei der Messung der Oberflachen Dosis der absorbierten Dosis in Abschnitten unterhalb der Oberflache und der Elektronen Tiefen Dosis in sowohl homogenen als auch inhomogenen absorbierenden Medien ist Die Messung einer vollstandigen Tiefendosis einschliesslich der Oberflacherdosis und der Dosis in Gebieten mit tiefen Gradienten wird durch Verwendung von Stapeln monokristallinischer Schichten von TLD 100 ermöglicht

RÉSUMÉ

Les auteurs présentent une méthode dosimétrique simple utilisant un scintillateur au LiF TLD 100 en couche monocristalline Cette technique est particulierement utile pour mesurer la dose en surface la dose absorbée dans la région au dessous de la surface et la dose d electrons en profondeur dans des absorbants homogenes et heterogenes La mesure d une courbe de dose en profondeur complete comprenant la dose en surface et la dose dans des regions de forts gradients est rendue possible par l utilisation de piles de couches monocristallines de TLD 100

REFERENCES

ALMOND P R, WRIGHT A and LONTZ J I The use of lithium fluoride thermoluminescent dosimeters to measure the dose distribution of a 15 MeV electron beam Phys in Med Biol 12 (1967) 389

ASHIN N BAKER R G and JOHNS H E Dose measurements in the build up region for Cobalt 60 radiation J Canad Ass Radiol 8 (1957) 72

BINKS C Energy dependence of lithium fluoride dosemeters at electron energies from 10 to 35 MeV Phys in Med Biol 14 (1969) 327

CAMERON J R, ZIMMERMAN D KENNY G, et coll Thermoluminescent radiation dosimetry utilizing LiF Hlth Phys 10 (1964) 25

DUTREIX J et DUTREIX A Etude comparée d une serie de chambres d ionisation dans des faisceaux d électrons de 20 et 10 MeV Biophysik 3 (1966), 249

HENDEE W R Thermoluminescent dosimetry of beta depth dose Amer J Roentgenol 97 (1966) 1045

— and KENNEDY K Thermoluminescent measurement of cellular radiation dose Amer J Roentgenol 100 (1967) 886

— GOLDEN R GARCIA C F et coll Depth dose measurements with lithium fluoride Amer J Roentgenol 102 (1968) 694

HOSPITAL PHYSICISTS ASSOCIATION A code of Practice for the dosimetry of 2 to 35 MV X ray and Cesium 137 and Co 60 Gamma ray beams Phys in Med Biol 14 (1969) 1

KARTHA M High energy electron dosimetry Doctorate thesis University of Western Ontario London Ontario Canada 1969

— A ferrous sulphate mini dosimeter Radiat Res 42 (1970) 220

— and MACDONALD J C F An automated thermoluminescent dose measuring system Presented at the Second Internat Conf Med Phys Boston U S A August 1969

KARZMARK C J WHITE J and FOWLER J F Lithium fluoride thermoluminescent dosimetry Phys in Med Biol 9 (1964) 273

LAUGHLIN J S LUNDY A PHILLIPS R et coll Electron beam treatment planning in inhomogenous tissue Radiology 85 (1965) 524

MACDONALD J C F A magnetic selected beta particle therapy unit for the treatment of superficial lesions Presented at the 11th Int Congress of Radiology Rome September 1965

NAYLOR G P Application of thermoluminescent phosphors in dosimetry problems in radiotherapy and radiobiology Brit J Radiol 40 (1967) 170

PINKERTON A P HOLT J G and LAUGHLIN J S Energy dependence of lithium fluoride dosemeters and high energy electron energies Phys in Med Biol 11 (1966) 129

ROBINSON J E and MCDOUGALL R S The use of a thermoluminescent dosemeter for dose measurements in the build up region (abstract) Phys in Med Biol 11 (1966) 145

SMITH I H MACDONALD J C F PFALZNER P M and FERGUSON H I S Cobalt 60 beam therapy Proc Second U N Conf on the Peaceful uses of Atomic Energy Geneva 1958 Vol 26 (1958) 295

SCRAD (The sub committee on Radiation Dosimetry) of the American Association of Physicists in Medicine Protocol for the dosimetry of high energy electrons Phys in Med Biol 11 (1966) 505

SUNTHARALINGAM N and CAMERON J R Thermoluminescent response of lithium fluoride to radiations with different LET Phys in Med Biol 14 (1969) 397

WORTON R G and HOLLOWAY A F Lithium fluoride thermoluminescence dosimetry Radiology 87 (1966) 938

ACTA RADIOLOGICA

OFFICIAL ORGAN OF THE RADIOLOGICAL SOCIETIES OF
DENMARK, FINLAND, NORWAY AND SWEDEN

Vol. 10 Fas. 3 — THERAPY PHYSICS BIOLOGY — 1971 June

RADIOBIOLOGIC DETERMINATION OF THE TOTAL DOSE IN RADIOTHERAPY

by

L. R. HOLSTI, P. M. RISSANEN and E. SPRING

The end result of radiotherapy depends on factors among which total dosage is most important. The direct cell action model derived from cell survival investigations in vitro and applied to tumour cell populations in vivo suggests that the dosages administered in radiotherapy are not sufficient to result in local neoplastic control. This is based on the assumption that if even a single tumour cell survives recurrence may develop. In clinical practice, however, 6 000 to 7 000 rad over 6 to 8 weeks of fractionated irradiation causes local cure of a significant number of neoplasms. There is thus some contradiction between the cell survival models and the results of clinical radiotherapy.

Physical treatment planning and dose determination are routine procedures in clinical radiotherapy. It has recently been reported (SPRING & MALMIO 1969) that iso-cell survival curves based on a single-hit multi-target model correspond with adequate accuracy to the isodose curves of the physical dose distribution. Given this, it is possible to examine the cell survival fractions instead of the radiation doses. The authors have applied this method in the present work to an autopsy material consisting of irradiated patients with carcinoma of the lung (RISSANEN et coll. 1968) in order to analyse the relations between the radiobiologic dose distribution and local cure against failure.

From the radiotherapy clinic (Director: Prof. L. R. Holsti), University Central Hospital, Helsinki, Finland. This investigation was supported by the Sigrid Juselius Foundation, Helsinki. Submitted for publication 29 June 1970.

Material and Methods

The material consisted of 57 histologically verified cases of inoperable carcinoma of the lung treated during the period 1963—1967 by megavoltage therapy and examined by autopsy 2 months to 4 years and 1 month (average 9 months) later (RISSANEN et coll) The histologic type was verified prior to treatment by biopsy in connection with bronchoscopy, tumour puncture, mediastinoscopy, scalenus biopsy or thoracotomy Together with roentgenography these methods were used also to determine the size and localization of the growth

Forty cases were treated with 33 MeV photons and 17 cases with a 3 000 curie ^{60}Co unit The weekly tumour dose was 1 000 to 1 100 rad and the tumour dosage ranged from 4 000 to 7 000 rad over 5 to 8 weeks Some of the cases were treated with the split course technique (HOLSTI 1969)

The findings have been divided into four groups according to the type of primary growth at autopsy (1) no carcinomatous tissue evident, (2) no definite malignancy macroscopically, but microscopically fibrosis with obvious islets of carcinoma cells, (3) necrotic areas with malignant infiltration, and (4) viable malignant tissue in the treatment area

1 *No carcinomatous tissue* Eighteen cases of the total series (18/57 = 32 per cent) had no carcinomatous tissue in the treatment area either macro- or microscopically Partial resection of the growth was performed in six and exploratory thoracotomy in two of these eighteen cases The tumour dose was 4 800 to 6 250 rad Fourteen (78 per cent) cases of this group were treated by the split course method and four received the entire course of irradiation as continuous therapy The pre planned treatment scheme was fulfilled in all the cases and there were no complications

2 *Fibrosis with islets of carcinoma cells* The group comprised nine cases (9/57 = 16 per cent) Partial resection of the tumour was performed in one and exploratory thoracotomy in another of these cases The dosage was 4 700 to 7 000 rad Four of these cases were treated by the split course method and five received continuous irradiation

3 *Necrotic areas containing carcinomatous tissue* The group comprised nine cases Treatment had to be discontinued in three, leaving only six (6/57 = 10 per cent) cases that received the planned dosage Three cases were subjected to exploratory thoracotomy The radiation dosage was 4 000 to 5 900 rad In only three cases was it possible to complete the therapeutic course according to schedule Six cases had complications (e g anemia, fever) necessitating interruption of the therapy Five cases were managed by the split course method and four cases received continuous treatment

4 *Viable carcinoma tissue in the treatment area* The fourth group comprised twenty-one cases Treatment had to be discontinued in four of them and thus viable carcinomatous tissue was demonstrable both macro- and microscopically in the treatment area in seventeen (17/57 = 30 per cent) cases that received roughly the planned dosage Exploratory thoracotomy was performed in three cases and partial resection of the tumour in one case The dosage was 4 000 to 6 000 rad The split course method was employed in eleven and continuous radiotherapy in ten cases The therapy was completed according to schedule in only eleven cases In the other ten complications (e g anemia fever) interfered with and in three of these prolonged the treatment time to 114 to 133 days

Metastases were demonstrated in fifty two cases of the total autopsy material

The single hit, multi target model

The main model used in radiotherapeutic calculations is the single hit multi target model, which means that the cells irradiated consist of m targets each of which must receive one hit to make the cell react, i e lose its reproductive integrity The following formula is then valid

$$S = 1 - (1 - e^{-D/D_0})^m \quad (1)$$

where S is the proportion of the cell population that survives the dose D (rad) and D_0 the 37 per cent dose the dose required to reduce the survival proportion to 37 per cent of its initial value (on the straight region of the logarithmic survival curve) The extrapolation number m may be considered as the average number of targets (sensitive sites) in the cell but should rather be regarded as a mathematical parameter with no morphologic or biochemical significance

It has been found that this formula provides a good description of the survival of a cell population given a single dose Usually m lies between 2 and 10, and D_0 between 100 and 180 rad for oxygenated cells For anoxic cells, D_0 increases to about 400 rad

If it is assumed that the parameters D_0 and m do not change during fractionated treatment (irradiation) the following formula may be applied for calculation of the cell survival fraction S at a particular point of the irradiated region

$$S = \prod_{i=1}^{i=n} \{1 - (1 - e^{-D_i/D_0})^m\} \quad (2)$$

where D_i (rad) is the dose delivered to the point at each irradiation

Most of the calculations in this work were performed with the parameters $D_0 = 160$ rad and $m = 2$ but these values are realistic only if the oxygen tension of the tumour tissue is assumed to be high during the whole treatment time

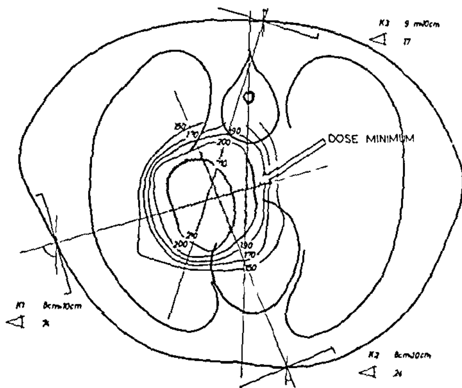


Fig. 1. Treatment plan with the point of dose minimum used in the calculations of cell survival fraction values. 33 MeV betatron photon treatment.

Experimental results of fractionated irradiation of tissues (FOWLER 1965, COHEN 1968) cannot properly be described with the assumption of constant values of D_0 and m (SPRING & HOLMBERG 1968, SPRING & PAASIKALLIO 1970). More realistic values are $D_0 = 300$ rad and $m = 1.5$. The lower D_0 value and the higher m value at the beginning of the treatment do not affect the final S values to such a degree that the S values obtained should be considered unrealistic.

Autopsy finding and survival fractions

The exact site of the treated region from which the autopsy findings were made was not known. The survival fraction values were therefore calculated for the point of the tumour where the dose had a minimum value (Fig. 1). Fig. 2 reveals that the calculated S value corresponds to the maximum survival fraction value (SPRING & MALMIO 1969).

The S values of the dose minimum point were calculated from formula (2) according to the treatment plan used.

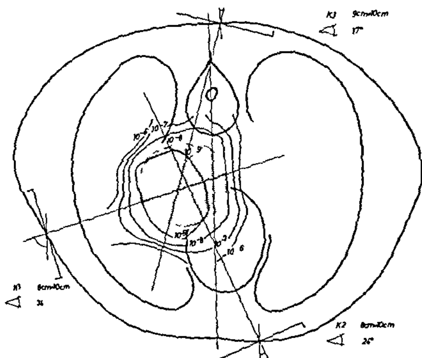


Fig 2 Radiologic treatment plan of the case of fig 1 The iso survival curves indicated in the figure are calculated with formula ( ) and the parameter values $D_0 = 160$ rad and $m = 2$ (SPRING & MATMO 1969) 33 MeV betatron photon treatment

The results obtained are presented graphically in Fig 3, grouped together into width classes of 10^{1} The figure includes the mean values of the logarithms of the survival fraction values They indicate that the mean value for the material where no carcinoma tissue was present at the primary tumour site was about 10^{1} lower than for the other material

The figure includes two boundary lines drawn from a closer analysis of the S values With the parameter values $D_0 = 160$ and $m = 2$ these boundaries are about 10 and 0.3×10^{8} The first value signifies that if the S value is higher than this boundary value malignant tissue always persists after the therapy in the region treated The S values calculated according to the treatment plan at the dose minimum point should therefore be lower than 10 to reach the region where complete destruction of the malignant tissue can be achieved The other boundary is about 0.3×10^{8} below which no malignant tissue was present at autopsy of the material examined This means that to destroy completely this tissue in the treated region the treatment plan must be drawn up in such a way

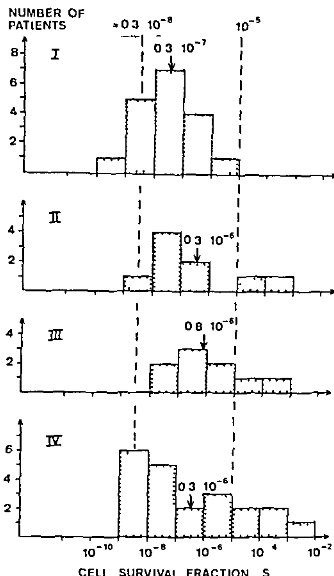


Fig 3 Distributions of the autopsy findings in various groups (I = no carcinomatous tissue II = fibrosis with islets of carcinoma cells III = necrotic areas containing carcinomatous tissue IV = viable carcinoma tissue in the treatment area) according to their corresponding cell survival fraction values calculated with formula (2) D_0 = 160 rad and m = 2

that the survival fraction value at the dose minimum point reaches a value lower than 0 3 × 10

The above mentioned boundary values are valid only if the calculations are made with formula (2) and $D_0 = 160$ rad and $m = 2$ As mentioned earlier, these values are assumed to be too optimistic in calculations of fractionated radio therapy Fig 4, which indicates schematically the probability of finding malignant tissue after the treatment in the cases of carcinoma of the lung in this investiga-

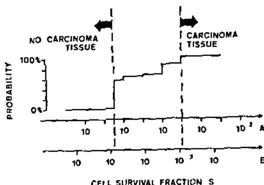


Fig 4 Graphic presentation of the findings indicating the propability of finding carcinoma tissue in the region treated after the therapy according to the corresponding calculated cell survival values The survival fraction values are arrived at with formula (?) with D_0 = 160 rad and m = ? (scale A) and D_0 = 300 rad and m = 1 5 (scale B)

tion has two scales A and B Scale A corresponds to calculation with the parameter values $D_0 = 160$ rad and $m = 2$, and scale B to those with $D_0 = 300$ rad and $m = 1\ 5$ It is assumed that the later scale gives a more realistic representation of the situation It indicates that even in cases in which 0 1 per cent of the malignant cells survive the irradiation no malignant tissue remains in the treated region after the termination of the therapy This explains perhaps the recovery of patients treated with 190 kV roentgen rays where the treatment plan takes account of a survival fraction of this magnitude (SPRING & MALMIO 1969)

Discussion and Conclusions

Most solid tumours in vivo are partially or wholly hypoxic (CLIFTON et coll 1966 THOMLINSON 1968) when of clinically detectable size, and few will be cured by radiotherapy based on predictions from cell survival curves Because it is possible after all to irradiate such growths with good results, other than direct effects of radiation on malignant cells may well have an influence on the response observed A variety of indirect effects may in fact contribute to the tumour response in vivo (MARUYAMA 1968) From the indirect effects (CLIFTON et coll MARUYAMA) solid tumour behaviour and response to radiation in human subjects are more complex than has been presumed from observations in cell cultures

The assumption that if one malignant cell remains alive after treatment the neoplasm may start to re grow and the treatment fails is less probable from the results obtained in this investigation It may be assumed that there is a boundary

value below which the cell survival fraction must go before the primary purpose of radiotherapy, the destruction of the malignant tissue, is achieved.

The results in this investigation more or less confirm that such boundary lines exist. Depending upon the parameter values for the 37 per cent dose and the extrapolation number in the calculation with formula (2), the boundary values are about 10^{-9} and 0.3×10^{-5} or 10^{-7} and 10^{-3}. The former values are obtained with $D_0 = 160$ rad and $m = 2$, and the latter with $D_0 = 300$ rad and $m = 1.5$. This investigation of cases of carcinoma of the lung indicates that the former value is the one below which the cell survival fraction must fall to make destruction of the tumour tissue at least possible. The latter value indicates the region where the tumour tissue is destroyed with high probability if the cell survival fraction value during the treatment sinks below the boundary value. This value, if known, may be used to calculate the total treatment dosage needed to reach a survival fraction value at which the tumour tissue in the region treated is probably destroyed.

It must be stressed that this is only one factor of the whole treatment, for so many others influence the success or failure of radiation therapy.

SUMMARY

Autopsy findings in carcinoma of the lung treated with megavoltage radiotherapy were analysed according to their calculated cell survival fraction values. The results indicate two boundary lines for cell survival values: the calculated value should be below the first line to give any probability at all, and below the second line to produce a high probability of no malignant tissue remaining in the region treated.

ZUSAMMENFASSUNG

Die Autopsiebefunde bei Carcinomen der Lunge, behandelt mit der Megavolt-Therapie, wurden im Hinblick auf die berechneten Fraktionen überlebender Zellen hin analysiert. Die Ergebnisse deuten auf zwei Grenzlinien für Zellüberlebenswerte hin: der berechnete Wert sollte unter der ersten Linie liegen, um überhaupt eine Wahrscheinlichkeit zu erhalten, und unter der zweiten Linie liegen, um eine hohe Wahrscheinlichkeit zu erhalten, dass nicht malignes Gewebe im Behandlungsgebiet übrig bleibt.

RÉSUMÉ

Les auteurs ont examiné les résultats d'autopsie dans le cancer du poumon traité par radiothérapie à mégavoltage en fonction des taux calculés de survie cellulaire. Les résultats mettent en évidence deux lignes limites de taux de survie cellulaire: le taux calculé devrait être au dessous de la première ligne pour donner une probabilité de disparition du tissu malin dans la région traitée et au dessus de la deuxième ligne pour donner une haute probabilité de disparition du tissu malin.

REFERENCES

CLIFTON K H BRIGGS R C and STONE H B Quantitative radiosensitivity studies of solid carcinomas in vivo Methodology and effect of anoxia J nat Cancer Inst 36 (1966) 965

COHEN L Theoretical iso-survival formulae for fractionated radiation therapy Brit J Radiol 41 (1968) 522

FOWLER J F The estimation of total dose for different numbers of fractions in radiotherapy Brit J Radiol 38 (1965) 365

HOLSTI L R Clinical experience with split-course radiotherapy A randomized clinical trial Radiology 92 (1969) 591

MARUYAMA Y Indirect effects of radiation upon tumor response in vivo A complex role Radiology 91 (1968) 657

RISSANEN P M TIKKA U and HOLSTI L R Autopsy findings in lung cancer treated with megavoltage radiotherapy Acta radiol Ther Phys Biol 7 (1968) 433

SPRING E and HOLMBERG P Evaluation of experimental irradiation fractionation with the single hit multi target model Acta radiol Ther Phys Biol 7 (1968) 297

— and MALMIO K Radiobiological treatment planning in radiotherapy Strahlentherapie 138 (1969) 662

— and PAASIKALLIO K Clinical and theoretical models in radiotherapy Strahlentherapie 140 (1970) 508

THOMLINSON R H Changes of oxygenation in tumours in relation to irradiation *In* Frontiers of radiation therapy and oncology Volume 3 p 109 Edited by J M Vaeth Karger Basel New York 1968

value below which the cell survival fraction must go before the primary purpose of radiotherapy, the destruction of the malignant tissue, is achieved

The results in this investigation more or less confirm that such boundary lines exist Depending upon the *parameter values for the 37 per cent dose* and the extrapolation number in the calculation with formula (2), the boundary values are about 10^{-6} and 0.3×10^{-8} or 10^{-5} and 10^{-9} The former values are obtained with $D_0 = 160$ rad and $m = 2$, and the latter with $D_0 = 300$ rad and $m = 1.5$ This investigation of cases of carcinoma of the lung indicates that the former value *is* the one below which the cell survival fraction must fall to make destruction of the tumour tissue at least possible The latter value indicates the region where the tumour tissue is destroyed with high probability if the cell survival fraction value during the treatment sinks below the boundary value This value, if known, may be used to calculate the total treatment dosage needed to reach a survival fraction value at which the tumour tissue in the region treated is probably destroyed

It must be stressed that this is only one factor of the whole treatment for so many others influence the success or failure of radiation therapy

SUMMARY

Autopsy findings in carcinoma of the lung treated with megavoltage radiotherapy were analysed according to their calculated cell survival fraction value The results indicate two boundary lines for cell survival values the calculated value should be below the first *line to give any probability at all* and below *the second line to produce a high probability* of no malignant tissue remaining in the region treated

ZUSAMMENFASSUNG

Die *Autopsiebefunde bei Carcinomen* der Lunge behandelt mit der Megavolt Therapie wurden im Hinblick auf die berechneten Fraktionen uber lebender Zellen hin analysiert Die Ergebnisse deuten auf zwei Grenzlinien fur Zelluberlebenswerte hin der berechnete *Wert sollte unter der ersten Linie liegen* um uberhaupt eine Wahrscheinlichkeit zu erhalten und unter der zweiten Linie liegen um eine hohe Wahrscheinlichkeit zu erhalten das nicht maligne Gewebe im Behandlungsgebiet ubrig bleibt

RÉSUMÉ

Les auteurs ont examiné les resultats d'autopsie dans le cancer du poumon traite par radiotherapie a mégavoltage en fonction des taux calculés de survie cellulaire Les résultats mettent en evidence deux lignes limites des taux de survie cellulaire le taux calculé devrait etre au dessous de la premiere ligne pour donner une probabilite de disparition du tissu malin dans la region traitee et au dessus de la deuxieme ligne pour donner une haute probabilité de disparition du tissu malin

REFERENCES

CLIFTON K H BRIGGS R C and STONE H B Quantitative radiosensitivity studies of solid carcinomas in vivo Methodology and effect of anoxia J nat Cancer Inst 36 (1966) 965

COHEN L Theoretical iso-survival formulae for fractionated radiation therapy Brit J Radiol 41 (1968) 522

FOWLER J F The estimation of total dose for different numbers of fractions in radiotherapy Brit J Radiol 38 (1965) 365

HOLSTI L R Clinical experience with split-course radiotherapy A randomized clinical trial Radiology 92 (1969) 591

MARUYAMA Y Indirect effects of radiation upon tumor response in vivo A complex role Radiology 91 (1968) 657

RISSANEN P M TIKKA U and HOLSTI L R Autopsy findings in lung cancer treated with megavoltage radiotherapy Acta radiol Ther Thys Biol 7 (1968) 433

SPRING E and HOLMBERG P Evaluation of experimental irradiation fractionation with the single hit multi target model Acta radiol Ther Phys Biol 7 (1968) 297

— and MALMIO K Radiobiological treatment planning in radiotherapy Strahlentherapie 138 (1969) 66?

— and PAASIKALLIO K Clinical and theoretical models in radiotherapy Strahlentherapie 140 (1970) 508

THOMLINSON R H Changes of oxygenation in tumours in relation to irradiation *In* Frontiers of radiation therapy and oncology Volume 3 p 109 Edited by J M Vaeth Karger Basel New York 1968

value below which the cell survival fraction must go before the primary purpose of radiotherapy, the destruction of the malignant tissue, is achieved

The results in this investigation more or less confirm that such boundary lines exist Depending upon the parameter values for the 37 per cent dose and the extrapolation number in the calculation with formula (2), the boundary values are about $10^{[illegible]}$ and 0.3×10^{-8} or 10^{-3} and $10^{[illegible]}$ The former values are obtained with $D_0 = 160$ rad and $m = 2$, and the latter with $D_0 = 300$ rad and $m = 1.5$ This investigation of cases of carcinoma of the lung indicates that the former value is the one below which the cell survival fraction must fall to make destruction of the tumour tissue at least possible The latter value indicates the region where the tumour tissue is destroyed with high probability if the cell survival fraction value during the treatment sinks below the boundary value This value, if known, may be used to calculate the total treatment dosage needed to reach a survival fraction value at which the tumour tissue in the region treated is probably destroyed

It must be stressed that this is only one factor of the whole treatment for so many others influence the success or failure of radiation therapy

SUMMARY

Autopsy findings in carcinoma of the lung treated with megavoltage radiotherapy were analysed according to their calculated cell survival fraction values The results indicate two boundary lines for cell survival values the calculated value should be below the first line to give any probability at all and below the second line to produce a high probability of no malignant tissue remaining in the region treated

ZUSAMMENFASSUNG

Die Autopsiebefunde bei Carcinomen der Lunge behandelt mit der Megavolt Therapie wurden im Hinblick auf die berechneten Fraktionen uber lebender Zellen hin analysiert Die Ergebnisse deuten auf zwei Grenzlinien fur Zelluberlebenswerte hin der berechnete Wert sollte unter der ersten Linie liegen um uberhaupt eine Wahrscheinlichkeit zu erhalten und unter der zweiten Linie liegen um eine hohe Wahrscheinlichkeit zu erhalten das nicht malignes Gewebe im Behandlungsgebiet ubrig bleibt

RÉSUMÉ

Les auteurs ont examine les resultats d autopsie dans le cancer du poumon traite par radiothérapie a mégavoltage en fonction des taux calculés de survie cellulaire Les résultats mettent en evidence deux lignes limites des taux de survie cellulaire le taux calcule devrait etre au dessous de la premiere ligne pour donner une probabilite de disparition du tissu malin dans la region traitee et au dessus de la deuxieme ligne pour donner une haute probabilite de disparition du tissu malin

rabbits implanted with Vx2 carcinoma (group D) For comparative purposes non irradiated, tumour bearing rabbits (group B), and tumour bearing rabbits irradiated with a single dose of 3 000 rad (group C) were also studied The doses were chosen on the basis of results from previous experiments with fractionated proton irradiation of Vx2 carcinoma in other organs In planning these and earlier experiments, the fractionation diagram by STRANDQVIST (1944) was used

Material and Methods Thirty rabbits were employed for the whole investigation and divided into four groups as shown below

Group and number of rabbits	Rabbit No	Tumour	Adsorbed dose (rad)				Total
A 8	I—VIII	—	1 750	1 750	1 750	1 750	7 000
B 6	IX—XIV	+					
C 8	XV—XXII	+	3 000				3 000
D 8	XXIII—XXX	+	1 750	1 750	1 750	1 750	7 000

The rabbits in group A had received no tumour but were repeatedly irradiated with a dose of 1 750 rad altogether with 7 000 rad in ten days

The rabbits in groups B C and D were injected with a suspension of Vx2 carcinoma (cf TJERNBERG 1962) into the muscles of the right chest wall on the mammillary line at the level of the 4th—5th ribs Twelve days after the carcinoma tran plantation the right chest region was irradiated in group C with 3 000 rad single do e and in group D 4 times with 1 750 rad at intervals of 3 days Irradiation was performed with the 185 MeV proton beam from the 230 cm synchrocyclotron under conditions described by DANIELSSON et coll (1971) The rabbits were strapped onto a Lucite stand which was placed horizontally at right angles to the axis beam with the ventral side of the animal facing the incoming beam The field measured 4 cm × 6 cm and by roentgenologic control the beam was o arranged that it covered the right half of the chest A ridge filter and water ab orber were u ed o that a 5 cm dose plateau contained the thickness of the animal from the ventral to the dorsal side of the chest

The do e rate in the plateau varied between 50 and 100 rad/min The animals were not anaesthetized but lay quite still during the treatment, this was checked by television The animals were observed carefully throughout the period of investigation and were weighed once weekly

Results

Group A This group consisted of eight adult rabbits without tumour irradiated four times with a dose of 1 750 rad at intervals of 3 days during 10 days (total dose 7 000 rad)

The weight curves of the rabbits are seen in Fig 1 They reflect in the main the condition of the animals Two rabbits (I and II) died 1 1/2 to 2 weeks after

FROM THE DEPARTMENTS OF PATHOLOGY II AND RADIOBIOLOGY, THE GUSTAF WERNER INSTITUTE, UNIVERSITY OF UPPSALA, SWEDEN

EFFECT OF SINGLE DOSE OR FRACTIONATED PROTON IRRADIATION ON PULMONARY TISSUE AND Vx2 CARCINOMA IN LUNG OF RABBIT

by

B ENGFELDT, B LARSSON, CHR NAESLUND, J NAESLUND and B TJERNBERG

In a previous paper (DANIELSSON et coll 1971) the effect of proton irradiation of one lung in the rabbit at a single dose of 3 000 rad was described Histologic examination after such irradiation revealed only minor injurious effects on the pulmonary tissue during an observation period of up to 12 months It seems on the other hand from earlier investigations on rabbits proton irradiated for Vx2 carcinoma implanted into the uterus (NAESLUND et coll 1959) or into the lower part of the anterior abdominal wall (DANIELSSON et coll 1968), that a single dose of 3 000 rad causes regression of the carcinoma A similar but slightly lower effect on Vx2 carcinoma was obtained with fractionated irradiation and a total dose of 6 000 rad given over five consecutive days Apparently complete regression of the tumour could be obtained on fractionated irradiation with a total dose of 8 000 rad

The effect of similarly fractionated proton irradiation of the lung with a total dose of 7 000 rad has now been studied *in healthy rabbits (group A) and in*

This work was supported by the Swedish Cancer Society Submitted for publication 20 April 1970

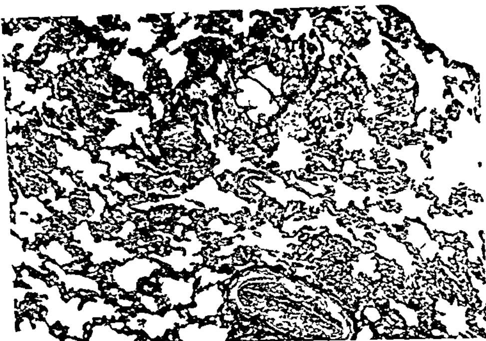
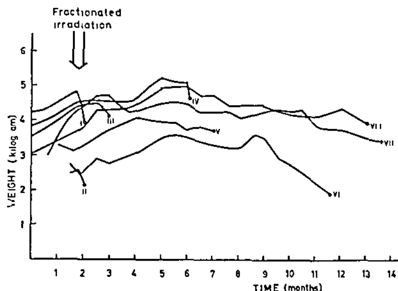


Fig 3 Microphotograph of lung from rabbit V group A 5 months after fractionated proton irradiation Some fibrosis is seen and also macrophages and lymphocytes Hematoxylin eosin ×120

changes which were more marked in the left lung In the skin within the irradiated region this rabbit exhibited necrosis and also inflammatory cell infiltration with histiocytic cells as well as incipient fibrosis in some areas

Rabbit IV one of the two that died after 4 to 5 months had at autopsy fibrosis in part of the irradiated right lung and both histiocytes and a number of round cells in the left lung there were oedema and atelectatic areas with inflammatory cell infiltrations The other animal rabbit V had in the right lung areas of fibrosis alternating with dilatation of the alveoli in some places hyalinization of connective tissue and close to these a number of macrophages and inflammatory cells Fig 3) The non irradiated lung exhibited collapsed areas with inflammatory cells in the alveoli as well as oedema but no hyalinization occurred

Similar changes were also seen at autopsy of rabbit VI, who lived for 10 months There were hyalinized areas in some places in the irradiated lung as well as diffusely collapsed alveoli within small regions Copious purulent exudate was seen in some of the main bronchi In the non irradiated lung there were areas containing collapsed parenchyma as well as histiocytic cells and a number of



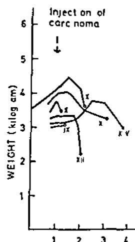


Fig. 1 (left). Weight curves for the animals in group A which were all given fractionated proton irradiation with 1 750 rad four times over ten days. ○ indicate rabbits who died. + the one that was killed.

Fig. 2 (right). Weight curves for the animals in group B which were implanted with Vx2 carcinoma but not irradiated. ○ indicate rabbits who died.

the first treatment. One rabbit (III) died after 7 weeks and two rabbits (IV and V) after 4 to 5 months. Two rabbits (VI and VIII) died after 10 to 11 months. One rabbit (VII) was killed after almost 12 months. The two rabbits that died within 2 weeks suffered a rapid decrease in weight before death. The body weight of the remaining animals increased during 3 to 4 months following irradiation but thereafter decreased, in general towards the end when the general condition also deteriorated.

A few weeks after irradiation all surviving rabbits exhibited epilation which became total and persisted on both the dorsal and ventral side of the chest throughout the period of observation. Several rabbits showed erythema, dermal necrosis and deep crusted ulcers predominantly in the dorsal region but in some cases also on the ventral side of the chest.

In rabbit I, who died 1 1/2 weeks after the first irradiation, autopsy revealed extensive necrosis, bronchopneumonia and pleuritic changes in the irradiated right lung. Bronchopneumonic changes were observed also in the non irradiated lung but there was no necrosis.

In rabbit II, who died after 2 weeks, autopsy revealed oedema in the alveoli of both lungs and congestion of the blood vessels. Rabbit III, who died after 7 weeks, also had pulmonary oedema and in addition scattered inflammatory

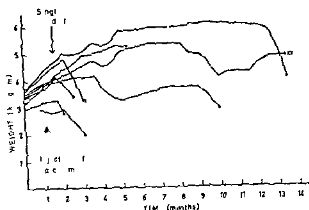


Fig 5 Weight curves for the animals in group C in which implantation of Vx2 carcinoma was followed by proton irradiation in a single dose of 3 000 rad ○ indicate rabbits who died + those that were killed

The weight curves of these rabbits are seen in Fig 2 Rabbits X and IX died 6 and 8 days after the injection Of the remainder rabbits XI and XII died after one month while XIII and XIV lived for respectively 2 and 2 1/2 months The weight of most of these animals decreased considerably during the period after injection and their general condition deteriorated gradually

Autopsy of rabbit IX revealed the presence of a few groups of carcinoma cells in the fat and connective tissue at the site of injection while no carcinoma cells were found at this location in rabbit X In the lungs no carcinoma was found in anyone of these rabbits but there was oedema and in places bronchopneumonia

In the other four rabbits a carcinomatous tumour which in some areas had become necrotic (Fig 4) was present at the site of implantation Two of the rabbits had metastatic carcinoma of the lung In one of these rabbits minor metastases were seen in the left lung and in the other the right lung was practically totally necrotic and definite carcinoma cells were present at the periphery There were also oedema and bronchopneumonic areas in the lungs of all these four rabbits

Group C This group of eight rabbits were injected with a suspension of Vx2 carcinoma into the musculature of the right chest wall and 12 days later they were proton irradiated with a single dose of 3 000 rad

The weight curves are shown in Fig 5 The weight of four of these rabbits, XVII XVI XV and XVIII began to decrease soon after irradiation, and the decrease continued until the animals died between 1 and 6 weeks later In the other four rabbits the body weight increased after irradiation Two of these

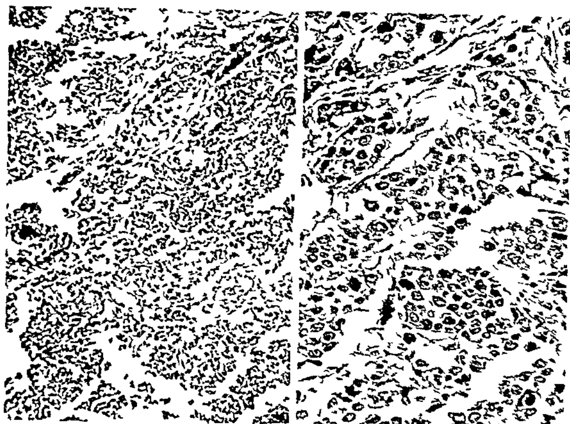


Fig. 4. Microphotographs of section from rabbit in group B, representing the site of implantation with growth of necrotizing, low differentiated squamous cell carcinoma. Hematoxylin-eosin. *Left* ×120, *right* ×450.

inflammatory cell elements. The skin in the irradiated region had very thin hyperkeratotic epidermis and highly sclerotic dermis.

Rabbit VII, who was killed almost one year after irradiation, had less marked changes but the right lung had areas of slight fibrosis with collapsed alveoli and in some places macrophages and several round cells. The left lung displayed no changes.

Rabbit VIII finally, who died 11 months after irradiation, had at autopsy fairly extensive collapsed areas and oedema in the irradiated right lung and in some places a large number of inflammatory cells. In addition, small areas were seen to contain proliferations of epithelium-like cell elements arranged in small groups with a suggestion, in places, of tubular differentiation. The left lung had moderate oedema and also alveoli containing an abundance of inflammatory cells.

Group B. The six rabbits of this group were injected with a suspension of Vx2 carcinoma simultaneously with the rabbits in groups C and D but were not subjected to irradiation.



Fig 7 Photomicrograph of section from part of the right lung in rabbit XXX of group D implanted with Vx2 carcinoma and proton irradiated with 1 750 rad four times over ten days The rabbit died 6 months after irradiation Hematoxylin eosin *Left* Destroyed lung parenchyma with fibrosis necrosis and proliferations of tubular adenomatous structures ×120 *Right* Details of the adenomatous structures ×450

lungs The irradiated right lungs in two rabbits also had small areas of hyaline fibrosis alternating with moderately emphysematous areas

Group D This group also consisted of eight rabbits After injection of Vx2 carcinoma into the right chest wall they were treated with fractionated proton irradiation receiving a dose of 1 750 rad every 3rd day starting 12 days after the tumour implantation The total dose amounted to 7 000 rad over ten days

Four rabbits died within 1 1/2 months after the first irradiation The remaining four rabbits lived for 6 to 8 months The weight curves are shown in Fig 6

About one month after treatment severe radiation damage in the form of complete epilation dermal necrosis and poorly healing ulcers with a crusted base

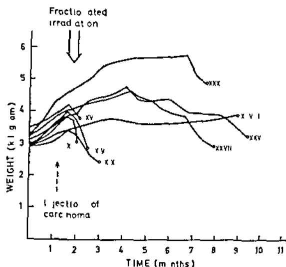


Fig 6 Weight curves for the animals in group D in which implantation of Vx2 carcinoma was followed by fractionated proton irradiation with 1 750 rad four times over ten days ◯ indicate rabbits who died

rabbits died after 4 (XIX) and 8 1/2 (XX) months while the other two were killed almost one year after irradiation

More or less marked epilation and slight epidermitis were observed in the irradiated area on the anterior side of the chest 1 to 2 months after irradiation Similar but more severe lesions occurred in the dorsal area, where superficial ulceration was also observed in some animals These changes gradually regressed however

Carcinoma was found at autopsy in two rabbits of this group In one, XVII, who died 1 1/2 weeks after irradiation, the irradiated right lung had some small microscopic tumour masses in the parenchyma, where small inflammatory in filtrations were also seen The right pleural surface was in addition coated with fibrin, and in places proliferation of fibroblasts in the thickened pleura was seen Large parts of the parenchyma in the non irradiated left lung displayed growth of necrotizing carcinoma of the squamous epithelial type Nothing pathologic was observed at the site of the carcinoma injection apart from epilation and thin squamous epithelium In the other rabbit, XVI, who died after one month, there was abundant growth of mainly necrotizing tumour tissue in the right lung Atelectases and a moderate amount of inflammatory cells were present in the left lung in addition to abundant growths of carcinoma which were also becoming necrotic The pleural surface was moderately infiltrated with a number of in flammatory cells Nothing pathologic was observed at the site of carcinoma im plantation

No carcinoma was found in the remaining rabbits neither in the region of the carcinoma implantation in the chest wall nor in the lungs Diffuse atelectatic areas and a large number of inflammatory cell infiltrations were seen in the

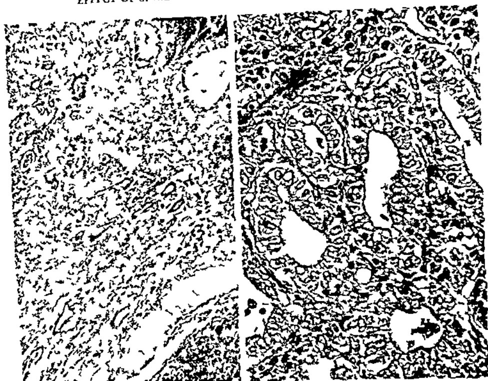


Fig Photomicrographs of section from part of the right lung in rabbit XXX of group D implanted with Vx2 carcinoma and proton irradiated with 1 750 rad four times over ten days The rabbit died 6 months after irradiation Hematoxylin eosin *Left* Destroyed lung parenchyma with fibrosis necrosis and proliferations of tubular adenomatous structures ×120 *Right* Details of the adenomatous structures ×450

lungs The irradiated right lungs in two rabbits also had small areas of hyaline fibrosis alternating with moderately emphysematous areas

Group D This group also consisted of eight rabbits After injection of Vx2 carcinoma into the right chest wall they were treated with fractionated proton irradiation receiving a dose of 1 750 rad every 3rd day starting 12 days after the tumour implantation The total dose amounted to 7 000 rad over ten days

Four rabbits died within 1 1/2 months after the first irradiation The remaining four rabbits lived for 6 to 8 months The weight curves are shown in Fig 6

About one month after treatment severe radiation damage in the form of complete epilation dermal necrosis and poorly healing ulcers with a crusted base

was noted in the irradiated area in all the animals both at the ventral and dorsal side of the chest These skin changes — which did not regress during the period of observation — were more marked in the dorsal region where the proton beam had emerged than on the ventral side of the chest

Carcinoma of the squamous epithelial type was found at autopsy in two animals of this group In one, rabbit XXIX who died 1 1/2 months after the first irradiation, a large necrotizing tumour was found in the area of the carcinoma injection in the chest wall but no carcinoma was seen in the lung parenchyma In the other animal, rabbit XXIII who died after 2 weeks, the irradiated right lung had extensive inflammatory changes and fibrinous pleuritis Several microscopic metastases were also found in the parenchyma of the left lung In a third animal, rabbit XXX who lived for 6 months, severe changes were seen at autopsy of the irradiated lung The pleura was thickened and coated with fibrin and inflammatory cells The pulmonary tissue was largely destroyed with fibrosis and a large number of macrophages as well as isolated giant cells Wide spread inflammatory cell infiltrations with both round cells and granulocytes were also present Large parts of the lung had in addition proliferations of a characteristic tumour like tissue, which was differentiated as small irregular tubuli, covered with simple, moderately polymorphous columnar epithelium (Fig 7) A number of atelectatic areas and also inflammatory infiltrations were present in the non irradiated left lung No proliferation of adenomatous type was however observed

In the other five rabbits (XXIV, XXI, XXVII, XXVIII and XXV), in whom no signs of carcinoma were observed, there were generally atelectatic and oedematous areas in the lungs as well as inflammatory cells in some areas In these rabbits, furthermore, there were in some places in the irradiated right lung small fibrotic areas with macrophages, round cells and hyalinized tissue The hyalinization had in some places changed to bone formation Some large arteries had thickened walls In the left lung there was only atelectasis and no fibrosis or macrophages

Discussion

Certain changes localized to the irradiated lung occurred in some of the rabbits of the experimental group A, in which the right lung was treated with proton radiation in fractions of 1 750 rad repeated four times at intervals of 3 days In two of the rabbits formations of hyalinized connective tissue and macrophages were seen in the irradiated right lung In one rabbit the right lung had areas with proliferation of epithelium like cell elements in the form of small groups or with suggestion of tubular structures These findings will be considered more in detail in connection with discussion of group D No such changes were found in the non irradiated left lung

No changes as those mentioned above were observed in the irradiated lung in the healthy rabbits treated once with a dose of 3 000 rad (DANIELSSON et coll 1971) If any conclusion might be drawn from these observations it would be that fractionated irradiation with a total dose of 7 000 rad, given as described, causes rather more definite damage to healthy pulmonary tissue than irradiation with a single dose of 3 000 rad The observations on the irradiated skin in the rabbits of group A also indicated that fractionated irradiation had a stronger effect than a single dose

The rabbits in groups B C and D were injected with a suspension of Vx2 carcinoma To judge from previous experience such a tumour transplant always survives and proliferates (TJERNBERG 1962 DANIELSSON et coll 1968)

The animals in group B which comprised six rabbits received only carcinoma injection and no irradiation Two rabbits died of respiratory infection as early as after 6 and 8 days All the others exhibited proliferation of carcinoma at the injection site but lived longer (two for one month one for two months and one for two and a half months) Carcinoma metastases were observed in the lungs in only two animals The survival time in this group was only slightly shorter than in a similar investigation comprising ten rabbits and in which most animals died within 2 months and all of them within 3 months (DANIELSSON et coll 1968)

The eight rabbits in group C after implantation were given proton irradiation with a single dose of 3 000 rad over the right chest wall Autopsy revealed carcinoma in the lungs of two animals In one of them the left lung had large carcinomatous areas in the right irradiated lung there were on the other hand only a few minor microscopic tumour masses In the other rabbit also autopsy disclosed an abundant growth of vital carcinoma in the non irradiated left lung while a highly necrotic carcinoma was present in the right lung Since no carcinoma was found in the region of tumour implantation neither in these two nor in anyone of the other rabbits in group C it would seem that proton irradiation in a single dose of 3 000 rad may be sufficient to produce regression of Vx2 carcinoma This irradiation did not appear to cause any noteworthy damage to other tissues Epilation occurred in the irradiated skin and in some cases ulcerations but the latter healed Atelecta is oedema and inflammatory cell infiltrations were generally seen in the irradiated lung and in two rabbits there were small areas of hyaline fibro is also in the right lung

In group D which comprised eight rabbits the carcinoma implantation was also followed by proton irradiation but in fractionated doses of 1 750 rad four times amounting to a total dose of 7 000 rad over ten days Squamous epithelial carcinoma occurred in two rabbits in this group in one of them at the site of implantation and in the other in the left lung A third rabbit exhibited epithelial

proliferations of another type, large parts of the right lung were in this animal found to be invaded by an adenomatous tumour like tissue which was differentiated *in the form of small irregular tubules* covered by simple, moderately polymorphous columnar epithelium The left lung had no such epithelial proliferation of adenomatous type Thus in both the groups of animals (A and D) which were treated with fractionated irradiation there was one animal with epithelium like proliferations which, in group D at least, were probably carcinomatous As to the histologic type *this tumour differed clearly from* an implanted carcinoma The histologic features of the tumour were similar to what in human pathology is sometimes called pulmonary adenomatosis and sometimes alveolar cell carcinoma, by which is usually meant a histologically benign variety of bronchiolar cancer There are however transitional forms but there are no definite histologic criteria *by which localized forms can be distinguished from the metastazing types* (LIEBOW 1952) *It may be of interest to consider that a similar histologic pattern has* been observed in an infectious, virus induced disease in sheep that is called jagziekte Metastasis has occurred in sheep with this disease It is probable that the high total dose attained by the prolonged irradiation of the lung in groups A and D *in some way facilitated the development of tumours This may have been* produced either by a direct effect on the lung tissue or, which is more likely, indirectly by the irradiation causing chronic, fibrosing pneumonitis, with epithelial proliferations subsequently changing into a tumourous state That irradiation induced pneumonitis in its chronic phases causes epithelial proliferation in the *finer bronchi is already known Such proliferations can be very extensive* (cf SPENCER 1962) The causal relationship in the present series between irradiation and the occurrence of epithelial proliferations must be a matter of further investigation

Apart from the changes mentioned there were in a number of rabbits from *group D minor lesions in the irradiated* right lung similar to those found in the animals of group A Thus, necrosis was seen in some places in the right lung of two rabbits and there were in addition in one of these rabbits hyalinized areas changing into bone formation and also wall thickening in some of the larger arteries No such marked changes were observed in the irradiated lung in the group of rabbits that were irradiated with a single dose These results conform with observations reported earlier (DANIELSSON et coll 1968) that fractionated irradiation with 6 000 rad, similarly applied, seems to have a stronger effect on healthy tissue than irradiation with 3 000 rad in a single dose

In spite of the apparently stronger effect on healthy tissue, fractionated irradiation did not seem to produce more definite regression of Vx2 carcinoma than irradiation with a single dose

SUMMARY

The effects of single dose and fractionated irradiation on the healthy lung and on Vx2 carcinoma implanted into the chest of adult rabbits were compared. Fractionated irradiation with a total dose of 7 000 rad over ten days seemed to produce more marked changes in the pulmonary tissue than irradiation with 3 000 rad in a single dose. Single dose irradiation appeared at least as effective on Vx2 carcinoma as the fractionated treatment. Marked changes in the form of circumscript fibrosis and in two animals near the fibrotic area moderately atypical proliferations of columnar epithelium were observed after fractionated irradiation of the lung of healthy and tumour bearing rabbits. The latter neoplastic formation was of tubular type and it seems probable that it had been caused directly or indirectly by the radiation treatment.

ZUSAMMENFASSUNG

Die Wirkung einer Einzelbestrahlung und fraktionierter Bestrahlung auf die gesunde Lunge und auf das Vx2 Karzinom implantiert in die Brust erwachsener Kaninchen wurde *verglichen*. Fraktionierte Bestrahlung mit einer Gesamtdosis von 7 000 rad uber zehn Tage verteilt *schien starkere* Veranderungen im Lungengewebe hervorzurufen als Bestrahlung mit 3 000 rad in einer Einzeldosis. Bestrahlung mit einer Einzeldosis erschien mindestens *ebenso* wirksam auf das Vx2 Karzinom zu sein wie fraktionierte Bestrahlung. Kraftige Veranderungen in Form einer umschriebenen Fibrose und in zwei Fallen in der Nahe des fibrotischen *Gebiets* massig atypische Proliferation des zylinderformigen Epithels wurden nach fraktionierter Bestrahlung *der Lunge gesunder* Kaninchen und Kaninchen mit Tumoren gefunden. Diese neoplastische *Veranderung* war von tubularem Typus und es erscheint wahrscheinlich, dass diese direkt oder indirekt durch die Strahlenbehandlung hervor*gerufen* war.

RÉSUMÉ

Les auteurs ont *compare l'effet* d'une dose unique et de l'irradiation fractionnee sur le poumon sain et sur *un cancer* Vx2 *greffe* dans le thorax de lapins adultes. L'irradiation fractionnee avec une dose totale *de 7 000 rad en* dix jours parait produire des lesions plus marquees dans le tissu pulmonaire que l'*irradiation par une* dose unique de 3 000 rad. L'irradiation par une dose unique parait au moins aussi efficace sur le cancer Vx2 que le traitement fractionne. *Des lesions marquees* sous la forme de fibrose circonscrite et chez deux animaux pres de la *région fibrosee* des proliferations moderement atypiques d'epithelium en colonne ont ete observ*ees apres* irradiation fractionnee du poumon de lapins sains et de lapins porteurs de tumeur. *Cette formation néoplasique* était de type tubulaire et il semble probable qu'elle avait ete causee directement ou indirectement par l'irradiation therapeutique.

REFERENCES

DANIELSSON, M., F. GRELOT, B. FORS, B. et coll.: Effect of high energy protons on Vx2 carcinoma implanted in the lower abdominal wall of the rabbits. Acta obstet. gynec. scand. 47 (1968) 373.

— — LARSSON, B. et coll.: Effects of therapeutic proton doses on organs in the neck, chest and upper abdomen. Acta radiol. Ther. Phys. Biol. 10 (1971) 21.

proliferations of another type, large parts of the right lung were in this animal found to be invaded by an adenomatous tumour like tissue which was differentiated in the form of small irregular tubules covered by simple, moderately polymorphous columnar epithelium. The left lung had no such epithelial proliferation of adenomatous type. Thus in both the groups of animals (A and D) which were treated with fractionated irradiation there was one animal with epithelium-like proliferations which, in group D at least, were probably carcinomatous. As to the histologic type this tumour differed clearly from an implanted carcinoma. The histologic features of the tumour were similar to what in human pathology is sometimes called pulmonary adenomatosis and sometimes alveolar cell carcinoma, by which is usually meant a histologically benign variety of bronchiolar cancer. There are however transitional forms but there are no definite histologic criteria by which localized forms can be distinguished from the metastazing types (LIEBOW 1952). It may be of interest to consider that a similar histologic pattern has been observed in an infectious, virus induced disease in sheep that is called Jagziekte. Metastasis has occurred in sheep with this disease. It is probable that the high total dose attained by the prolonged irradiation of the lung in groups A and D in some way facilitated the development of tumours. This may have been produced either by a direct effect on the lung tissue or, which is more likely, indirectly by the irradiation causing chronic, fibrosing pneumonitis with epithelial proliferations subsequently changing into a tumourous state. That irradiation induced pneumonitis in its chronic phases causes epithelial proliferation in the finer bronchi is already known. Such proliferations can be very extensive (cf. SPENCER 1962). The causal relationship in the present series between irradiation and the occurrence of epithelial proliferations must be a matter of further investigation.

Apart from the changes mentioned there were in a number of rabbits from group D minor lesions in the irradiated right lung similar to those found in the animals of group A. Thus, necrosis was seen in some places in the right lung of two rabbits and there were in addition in one of these rabbits hyalinized areas changing into bone formation and also wall thickening in some of the larger arteries. No such marked changes were observed in the irradiated lung in the group of rabbits that were irradiated with a single dose. These results conform with observations reported earlier (DANIELSSON et coll. 1968) that fractionated irradiation with 6 000 rad, similarly applied, seems to have a stronger effect on healthy tissue than irradiation with 3 000 rad in a single dose.

In spite of the apparently stronger effect on healthy tissue fractionated irradiation did not seem to produce more definite regression of Vx2 carcinoma than irradiation with a single dose.

SUMMARY

The effects of single dose and fractionated irradiation on the healthy lung and on Vx2 carcinoma implanted into the chest of adult rabbits were compared Fractionated irradiation with a total dose of 7 000 rad over ten days seemed to produce more marked changes in the pulmonary tissue than irradiation with 3 000 rad in a single dose Single dose irradiation appeared at least as effective on Vx2 carcinoma as the fractionated treatment Marked changes in the form of circumscript fibrosis and in two animals near the fibrotic area moderately atypical proliferations of columnar epithelium were observed after fractionated irradiation of the lung of healthy and tumour bearing rabbits The latter neoplastic formation was of tubular type and it seems probable that it had been cau d directly or indirectly by the radiation treatment

ZUSAMMENFASSUNG

Die Wirkung einer Einzelbestrahlung und fraktionierter Bestrahlung auf die gesunde Lunge u d auf das Vx2 Karzinom implantiert in die Brust erwachsener Kaninchen wurde erglichen Fraktionierte Bestrahlung mit einer Gesamtdosis von 7 000 rad über zehn Tage verteilt schien starkere Veranderungen im Lungengewebe hervorzurufen als Bestrahlung mit 3 000 rad in einer Einzeldosis B strahlung mit einer Einzeldosis erschien mindestens ebenso wirksam auf das Vx2 Karzinom zu sein wie fraktionierte Bestrahlung Kraftige Verande rungen in Form einer umschriebenen Fibrose und in zwei Fallen in der Nahe d s fibroti schen Gebiets massig atypische Proliferation des zylinderformi en Epithels wurden nach fraktionierter Bestrahlung der Lunge gesunder Kaninchen und Kaninchen mit Tumoren ge funden Die e neoplasti che Veranderung war von ubularem Typus und es erscheint wahr scheinlich dass diese direkt od r indirekt durch die Strahlenbehandlung hervorgerufen war

RÉSUMÉ

Les auteurs ont compare l effet d une dos unique et de l irradiation fractionnee sur le poumon sain et sur un cancer Vx2 greffe dans le thorax de lapins adultes L irradiation fra tionnee a ec une dose totale de 7 000 rad en dix jours parait produire des lesions plus marquees dans le tissu pulmonaire que l irradiation par une dose unique de 3 000 rad L irradiation par une dose unique parait au moins aussi efficace sur le cancer Vx2 que le traitement fractionne Des lesions marquées sous la forme de fibrose circonscrite et chez deux animaux pres d la région fibro ee des proliferati ns moderement atypiques d epithe lium en colonne ont ete observees apres irradiation fractionnee du poumon de lapins sains et de lapins porteurs de tumeur Cette formation néoplasique etait de type tubulaire et il emble probable qu elle avait été causee directement ou indirectement par l irradiation therapeutique

REFERENCES

DANIELSSON M ENGFELDT B FORS B et coll Effect of high energy protons on Vx2 carcinoma implanted in the lo er abdominal wall of the rabbits Acta obstet gynec scand 47 (1968) 373

— — LARSSON B et coll Effects of therapeutic proton doses on organs in the neck chest and upper abdomen Acta radiol Ther Phys B ol 10 (1971) 215

FALKMER S FORS B LARSSON B et coll Pilot study on proton irradiation of human carcinoma Acta radiol 58 (1962), 33
FORS B LARSSON B LINDELL A et coll Effect of high energy protons on human genital carcinoma Acta radiol Ther Phys Biol 2 (1964) 384
LIEBOW A A Atlas of tumour pathology Section V Fasc 17 p 53 Washington D C 1952
NAESLUND J STENSON S and LARSSON B Results of proton irradiation of Vx2 carcinoma in the uterus of rabbits Acta obstet gynec scand 38 (1959) 563
SPENCER H Pathology of the lung p 373 Pergamon Press London 1962
STRANDQVIST M Studien uber die kumulative Wirkung der Rontgenstrahlen bei Fraktionierung Acta radiol (1944) Suppl No 55
TJERNBERG B Lymphography An animal study on the diagnosis of Vx2 carcinoma and inflammation Acta radiol (1962) Suppl No 214

FROM THE LABORATORY OF EXPERIMENTAL BIOLOGY, DEPARTMENT OF ANATOMY, UNIVERSITY OF GOTHENBURG AND THE DIVISION OF EXPERIMENTAL DEFENCE MEDICINE RESEARCH INSTITUTE OF NATIONAL DEFENCE, SUNDBYBERG SWEDEN

MICROVASCULAR PERMEABILITY IN IRRADIATED RABBITS

by

G LUNDBORG and B SCHILDT

BELFRAGE & SCHILDT (1967) observed increased sensitivity to succinylcholine (SCh) in animals subjected to whole body irradiation while investigating the effect of SCh on the neuromuscular transmission in normal and irradiated rabbits These experiments indicated that SCh had a cumulative effect in the latter Among the possible mechanisms involved in this phenomenon impaired peripheral circulation secondary to microvascular irradiation injury was suggested as the cause A subsequent investigation on the flow perfusion rate of muscle tissue in the hindlimbs of rabbits failed however to reveal any significant difference between irradiated and normal animals (BELFRAGE & SCHILDT 1968) The present investigation was therefore carried out to analyse further the microvascular response to irradiation with special reference to the permeability of macromolecules

Varying degrees of vascular damage have often been demonstrated in different tissues following irradiation (cf p 316) The permeability of the vessels of the peripheral nerves has been analysed following injuries other than those due to

Submitted for publication 30 September 1970

irradiation by, e g MELLICK & CAVANAGH (1967), OLSSON (1966), LUNDBORG (1970) The latter used fluorescence microscopy tracings of intravenously injected serum albumin, tagged with Evans blue, to demonstrate changes of the permeability in microvessels of the rabbit s tibial nerve previously subjected to ischemia This method has been used in the present investigation to evaluate the injury induced to endoneurial microvessels by irradiation A slight, controlled ischemic injury was added to the limb to produce subliminal vessel injuries not detectable by the tracer technique per se This strategy was based on the findings of LUNDBORG (1970) that ischemia of 8 to 10 hours duration is necessary for causing damage to endoneurial vessels

Material and Methods The experiments were performed in 40 male rabbits (small chinchilla) 3 to 4 months of age and of about uniform weight (3 0 ± 0 4 kg) The experiments involved three procedures (cf Table) (1) whole body irradiation of the rabbits, (2) induction of ischemia in one hind limb for 2 hours at intervals of 1 to 16 days, and (3) analysis of microvascular permeability in both hind legs subsequent to the ischemic period

The animals were roentgen irradiated (Muller MG 300) two by two at 280 kV and 11 mA, the dose rate being 20 R/min with a total dose of 1 100 R, constituting approximately the LD_{50} for the strain (SCHILDT & SCHILDT 1963) The examinations were performed 1, 4, 8, 12 and 16 days after irradiation The animals were anaesthetized intravenously with 30 mg/kg sodium pentobarbital (Nembutal) with additional small doses during the experiments Before injection of the tracer substance, ischemia was induced in one hind limb for two hours by applying an infant s pneumatic cuff around the thigh of the rabbit and inflating it to about 700 mm Hg, this caused complete stagnation of flow in the intraneural microvessels as previously demonstrated by LUNDBORG (1970)

Changes in the vascular permeability of the tibial nerve were demonstrated by fluorescence microscopy tracings of intravenously injected serum albumin tagged with Evans blue The tracer solution was prepared by mixing in vitro bovine serum albumin 5 % with Evans blue by the method of STEINWALL & KLATZO (1965) and OLSSON (1966) The conjugate was carefully filtrated before use through a Sephadex column for removal of free tracer The standard dose was 1 ml labelled albumin 5 % solution per 100 g body weight This solution was slowly intravenously injected into an ear vein immediately after release of the cuff The animals were killed 30 minutes after the injection by rapid infusion of an overdose of sodium pentobarbital (Nembutal) and specimens from the tibial nerve of both legs were taken for examination the one from the leg subjected to both irradiation and ischemia will be called the experimental nerve and the other (irradiation only) the control nerve The nerve specimens were

Table

Summary of investigation and findings

Group (n)	Treatment		Time after irradiation (days)	Petechial bleedings*	Increased permeability**
	Irradiation (R)	Ischemia (hours)			
A	—	—	—	0	0
(7)					
B	—	2	—	0	0
(6)					
C	1100	—	1	0	0
(4)	1100	2	1	+	+
D	1100	—	4	0	0
(6)	1100	2	4	++	+
E	1100	—	8	0	0
(7)	1100	2	8	+++	+++
F	1100	—	12	0	0
(5)	1100	2	12	+	++
G	1100	—	16	0	0
(5)	1100	2	16	0	0

* Grading of bleedings in skin and tibial nerve 0 = not present + = rare and spotted ++ = = numerous but spotted +++ = numerous and general

** Grading of increased permeability as indicated by extravascular leakage of tracer 0 = not present + = moderate and spotted ++ = moderate and general +++ = massive and general

fixed in formalin 5 % solution for 24 hours Frozen longitudinal sections of 10 mu thickness were mounted in aqueous glycerine 50 % and immediately examined in a Leitz fluorescence microscope equipped with a dark field condenser and an Osram HBO 200 W high pressure mercury lamp The light was directed through a Schott BG 12/3 mm filter the light emitted was passed in the tubes through a K 510 filter Under these conditions Evans blue albumin emits a bright red fluorescence (cf the Figure) and intravascular or extravascular tracing of the conjugate may easily be performed

Results

The results are summarized in the Table and Figure The changes reported below were generally very much the same for each experimental group (A—G)

A Unirradiated non ischemic control nerves ($n = 7$) No obvious blue staining was evident Fluorescence microscopy No extravascular red fluorescence was ever observed accordingly no leakage of Evans blue albumin into the endoneurial space was evident (cf Figure a)

B Unirradiated, ischemic (2 hrs) control nerves (n = 6) No obvious blue staining of the nerves, no bleeding detected at any level Fluorescence microscopy No extravascular red fluorescence was apparent in the endoneurial space, the conjugate being strictly confined to the lumen of the endoneurial blood vessels (cf Figure a)

C One day after irradiation (n = 4) The nerve from the experimental limbs exhibited considerable blue staining and spotted bleeding of varying degree was occasionally apparent at varying levels along the nerve The nerves from the control limb always presented normal appearances Fluorescence microscopy The experimental nerves displayed spotted extravascular leakage of tracer, the red fluorescence presenting an irregular diffuse distribution in the endoneurial space Large areas of the nerve were, however, not subjected to the leakage, in these parts the red fluorescence was completely confined to the vessel lumen The nerve from the control limbs never had any extravascular leakage of albumin

D Four days after irradiation (n = 6) The experimental nerves presented strong blue staining, and at all levels there were numerous areas of slight bleeding The nerves from the control limbs always had normal appearances Fluorescence microscopy Like the nerves prepared 1 day after irradiation, diffuse red fluorescence was present at most levels in the endoneurium Some areas did not, however, appreciably differ from the control nerves The latter never presented any extravascular red fluorescence

E Eight days after irradiation (n = 7) These rabbits invariably had numerous spots of slight bleeding on both hind limbs in skin areas that had been subjected to hair clipping prior to examination The experimental nerve displayed numerous large areas of bleeding at all levels while no such phenomena were apparent in the control nerves Fluorescence microscopy Specimens from the experimental nerves had strong diffuse red fluorescence in all parts of the endoneurium, indicating a general leakage of albumin (cf Figure c) The control nerves never had extravascular red fluorescence (cf Figure b)

F Twelve days after irradiation (n = 5) In two of the animals, scattered areas of bleeding occurred in the skin on limbs subjected to hair clipping Small areas of bleeding could occasionally be observed in the tibial nerve of the experimental side The control nerve was normal in appearance Fluorescence microscopy Extravascular red fluorescence of varying intensity was apparent at all levels of the experimental nerves The red fluorescence was confined to the lumen of the endoneurial vessels in the control nerves

G Sixteen days after irradiation (n = 5) No bleeding occurred in the skin on limbs subjected to hair clipping neither could any bleeding be observed in the tibial nerve of either limb Fluorescence microscopy No extravascular red fluorescence could be detected in the experimental or in the control nerves



a) Control nerve from an untreated rabbit The tracer (yellow red) is strictly confined to the lumen of endoneurial blood vessels Marked fibre structure of the fascicle (green)



b) Tibial nerve from left limb of a rabbit treated by total body irradiation 8 days previously The limb was not subjected to ischemia before injection of the tracer The Evans blue albumin is still strictly confined to the vessel lumen no extravascular leakage being evident



c) Tibial nerve from right limb of the same rabbit as in (b) The limb was further subjected to 2 hours ischemia before injection of the tracer Marked leakage of tracer the red fluorescence being diffusely distributed in the endoneurium

Distribution of Evans blue albumin in the tibial nerve of rabbits under various experimental conditions as revealed by fluorescence microscopy

Discussion

Interest has previously been focussed upon the behaviour of the endoneurial microvessels following various kinds of injuries (OLSSON 1966 MELLICK & CAVANAGH 1967 LUNDBORG 1970) The effects of irradiation on the permeability of these vessels have however, not been investigated A new feature is the addition to the radiation injury of a second light injury (in this case ischemia) which in itself is incapable of producing any detectable damage to the vessel walls This method is thought to be a useful approach to problems concerning early micro vascular changes It also illustrates the important fact that two different types of injuries have a synergistic effect when combined (SCHILDT & THOREN 1968) The endoneurial vessels of the irradiated limbs not being subjected to ischemia failed to reveal any leakage of tracer albumin In the legs kept ischemic for 2 hours however leakage was detectable as early as 24 hours following irradiation The radiation damage could thus not be detected by the tracer technique per se but became apparent after the addition of a very slight endothelial injury corresponding to 2 hours ischemia Since LUNDBORG (1970) has reported that as much as 8 to 10 hours ischemia is required to cause permeability disturbances, this short ischemia can in itself only have caused insignificant damage to the vessel walls

Regarding the time interval between the exposure and the appearance of permeability disturbances the present results indicate that an increased permeability is apparent on the 4th day reaches a maximum around the 8th day and persists for about 2 weeks after irradiation These findings are in line with several previous investigations that indicate the existence of a peak in microvascular permeability 1 to 2 weeks after exposure (FURTH et coll 1951, WISH et coll 1952 CRONKITE & BOND 1960 VARTERESZ 1966 ARTURSON & THOREN 1968)

Considerable discrepancy exists regarding the exposure dose needed to inflict significant damage to the blood vessels Generally speaking the vascular tree is considered relatively radioresistant According to RHOADES (1948) supralethal doses are required to produce recognizable structural disintegration of the endothelial cells It has been stated that with doses around LD 50 the endothelium is rarely affected CRONKITE & BOND (1960) reported that irradiation doses of 1 500 R are necessary to cause detectable changes From the present and from many previous investigations however it appears obvious that functional disturbances occur in the microvascular endothelium at considerably lower doses Thus doses corresponding to LD 50 have been found to induce detectable general disturbances in microvascular permeability (FURTH et coll 1951 WISH et coll 1952) Investigations involving histologic examination of the sciatic nerve in rabbits after local irradiation with 30 krad by BERGSTROM (1962) revealed that the endothelium was still intact after 5 to 7 days

posure dose and the time lapse after irradiation The capillary leakage was greate t 2 weeks after irradiation With 1 000 R, the CL/CP ratio was close to zero for dextran with a molecular weight of approximately 70 000 i e molecules of the same size as serum albumin failed to pass the capillary walls which is in agreement with the present findings The capillaries possessed however an in creased permeability for maller molecules as compared to non irradiated con trols Larger and larger dextran molecules passed the blood lymph barrier in dicating definite damage in paws exposed to 200 to 4 000 R

The non specific effect of ionizing radiation should be emphasized The micro-vascular reactions that characterize the early changes of inflammation are re markably similar in different kinds of injuries and include vasodilatation in creased permeability and migration of leukocytes Such changes may arise fol lowing for instance chemical injury ionizing radiation local anaphylaxis me chanical trauma thermal trauma, ultraviolet light injury (SCHILDT & ARTUR SON 1970)

The considerable increase in vascular permeability to fluids electrolytes and proteins may be due either to increased hydrostatic pressure in the microvessels or damage to the endothelial barrier itself These changes may in turn be caused by physical effects or mediated by endogenous substances released or activated by the injury

Regarding the physical effects three mechanisms are thought to govern the tran fer of materials across the capillary membranes (1) diffusion for small molecules (2) ultrafiltration and more recently (3) pinocytosis for larger mole cules Larger molecules such as those of dextran or albumin are transported in bulk through a few capillary leaks with a radius of about 250 Å (GROTTE 1965) The increased permeability after different injuries including irradiation is according to ARTURSON (1970) due to an increase in the size of these leaks This has been called the stretched pore phenomenon and is localized anatomi cally to the venular side it seems to act as a safety valve by letting out puffs of the intravascular content into the extravascular compartment

Damage to the intercellular substance is often given as an explanation of the increased capillary permeability present after irradiation as well as following other types of injuries According to VARTERESZ (1966) and others hyaluronic acid is depolymerized in vitro by irradiation already at low dose levels It is split by hyaluronidase into glucuronic acid and acetyl glucose amine Irradiation ac tivates hyaluronidase in vitro but final evidence that this occurs in vivo as well is at present lacking

Mo t workers ascribe increased permeability chiefly to the existence of endo genous mediators A great number have been suggested but only a few have tood critical examination Among the latter are histamine serotonin and various

The present investigations indicated that exposure to 1 100 R caused no obvious damage but the existence of a subliminal endothelial damage could be demonstrated by the addition of slight ischemia.

Several reports indicate a difference in radiosensitivity among arteries, veins and capillaries with regard to morphologic changes. LINSER (1905) could find no endothelial damage in the arteries or veins after irradiation, while the endothelium of the arterioles was either absent or swollen and projected into the lumen. On the other hand, LAZARUS BARLOW (1922) reported that the arterioles were the only vessels escaping damage from gamma irradiation. Another view was presented by LISKIND (1940), who described radioresistance of endothelial cells in larger vessels but reported signs of cellular injury in the endothelium of smaller vessels. This view has been supported by others, e.g. RUBIN & CASARETT (1968).

The great variation in the results is apparently due to differences in the type, energy and dose of irradiation, the time lapse after exposure before examination, and species differences.

Most of the interest regarding radiation induced damage to blood vessels has been focussed on the endothelium. Its swelling and proliferation, in certain conditions prominent enough to obliterate capillaries, have been reported (e.g. PORTER & WHITE 1907, WOLBACH 1925, ELLINGER 1935). CRONKITE & BOND (1960) also pointed to endothelial swelling as a characteristic feature together with degeneration of the smooth muscle and connective tissue coat of the blood vessels, particulary of the capillaries, such as increased permeability, have been demonstrated by several authors. PAINTER et coll. (1947), who injected Evans blue into rabbits subjected to local irradiation, reported that the dye appeared more rapidly in irradiated than in non irradiated areas. A rapid disappearance of labelled proteins, erythrocytes or Evans blue from the circulation of irradiated (LD_{50}) rabbits has been reported by FURTH et coll. (1951) and WISH et coll. (1952). *Increased vascular permeability* was observed in dogs by CHERNOV et coll. (1965) as early as 24 hours after exposure to 600 R (LD_{100}) as indicated by an increased disappearance rate of intravenously injected fluorescein compared to controls. The permeability of the skin capillaries increased in dogs exposed to 500 R as reported by VARTRESZ (1966). A more sensitive method was used by ARTURSON & THOREN (1968), who investigated the capillary permeability following local irradiation (200 to 4 000 R) of the paws of dogs by measuring the leakage of dextran molecules across the blood lymph barrier. The draining lymphatics of the paws were cannulated and dextran of varying molecular size injected intravenously. The lymph to plasma concentration ratio (CL/CP) of the dextran was then determined. These authors found sieving characteristics of the blood lymph barrier in irradiated tissue to be correlated to both the ex

REFERENCES

ANGGÅRD E, ARTURSON G and JONSSON C E Efflux of prostaglandins in lymph from scolded tissu (Abstract) Acta physiol scand 80 (1970) 46

ARTURSON G Personal cummunication 1970

— and THOREN L Capillary permeability following ionizing radiation p 83 In Combined injuries and shock Edited by B Schildt and L Thorén Almqvist & Wiksell Stockholm 1968

BELFRAGE P and SCHILDT B Increased sensitivity to the muscle relaxing effect of succinyl choline Acta anaesth scand 11 (1967) 65

— — Muscle blood flow in whole body irradiated rabbits Res Inst Nat Def (Stockholm) Report C 1783—27 (1968)

BERGSTROM R Changes in peripheral nerve tissue after irradiation with high energy protons Acta radiol 58 (1962) 301

CHERNOV G A SHEREMET Z I and LENSKYA R Effect of irradiation on vascular permeability and on blood mucopolysaccharide and serotonin levels Fed Proc 24 (1965) 974

CRONKITE E P and BOND V P Radiation injury in man Charles C Thomas Springfield Illinois 1960

ERSKIND L Vaskulare Veranderungen nach intravenoser Injektion von Thoriumdioxyd (Thorotrast) Acta chir scand 84 (1940) 177

ELLINGER F Die biologischen Grundlagen der Strahlenbehandlung ein Lehrbuch für Studierende und Ärzte Sonderbande zur Strahlentherapie 20 (1935) 1

FURTH F ANDREWS G A STOREY R H and WISH L The effect of x irradiation on erythrogenesis plasma and cell volumes Sth med J (Bgham Ala) 44 (1951) 85

GROTTE G Passage of dextran molecules across capillary walls Acta chir scand (1956) Suppl No 211

LAZARUS BARLOW W S On the histological and some other changes produced in animals by exposure to the gamma rays of radium Spec Rep Ser med Res Coun (Lond) No 6? (192?) 33

LINSER P Beitrag zur Histologie der Rontgenwirkung auf die normale menschliche Haut Fortschr Rontgenstr 8 (1905) 97

LUNDBORG G Ischemic nerve injury Experimental studies on intraneural microvascular pathophysiology and nerve function in a limb subjected to temporary circulatory arrest Scand J plast Reconstr Surg (1970) Suppl No 6

MELLICK R and CAVANAGH J B Longitudinal movement of radioiodinated albumin within extravascular spaces of peripheral nerves following three systems of experimental trauma J Neurol Neurosurg Psychiat 30 (1967) 458

OLSSON Y Studies on vascular permeability in peripheral nerves II Distribution of circulating fluorescent serum albumin in rat sciatic nerve after local injection of histamine 5-hydroxytryptamine and compound 48 80 Acta physiol scand 69 (1966) Suppl No 284

PAINTER E E PROSSER C L and MOORE M C Physiolog cal observation on rabbits exposed to single doses of x rays USAEC (1947) Report MDDC 761

PORTER C A and WHITE C J Multiple carcinomata following chronic X ray dermatitis Ann Surg 46 (1907) 649

RHOADES R F The vascular system In Histopathology of irradiation from external and internal sou ces Edited by W Blom McGraw Hill Book Co New York 1948

RUBIN P and CASARETT G W Clinical radiation pathology W B Saunders Company Philadelphia London and Toronto 1968

SCHACHTER M Kallikreins and kinins Physiol Rev 49 (1969) 509

proteases (WILHELM 1962, SCHACHTER 1969) and recently prostaglandin (ANGGARD et coll. 1970).

Conclusion

Whole body ionizing radiation around LD_{50} evidently may increase the permeability of microvessels to macromolecular substances. The nature of this is not clear, but resembles closely the increased permeability evident after other types of *injuries. The reactions are nonspecific and apparently not governed by* the type of injury in the first place, but rather by the ability of the exposed cells *to react*. The factors involved are (not in order of importance): leaks in the vessel wall, changes in the intercellular substance and the existence of endogenous mediators such as histamine, serotonin, proteases and prostaglandin.

SUMMARY

The microvascular permeability of the endoneurial vessels of the tibial nerve was investigated in rabbits exposed to 1 100 R roentgen irradiation, corresponding to LD_{50}. Radiation damage was not detected following the tracer technique per se. The addition of slight ischemic injury, not capable in itself of causing permeability disturbances, revealed however vascular damage during the first two weeks following irradiation.

ZUSAMMENFASSUNG

Die mikrovaskuläre Permeabilität der endoneuralen Gefässe des Nervus tibialis des Kaninchens wurde nach Bestrahlung mit 1 100 R Röntgenstrahlung entsprechend der LD_{50} untersucht. Der Strahlenschaden war per se mit *Hilfe* der Spurentechnik nicht nachweisbar. Wurde zusätzlich ein leichter ischämischer Schaden hinzugefügt, der selbst nicht zu *Permeabilitätsänderungen führte, wurde jedoch ein klarer vaskulärer Schaden* während der zwei ersten Wochen nach der Bestrahlung deutlich.

RÉSUMÉ

Les auteurs ont *étudié la perméabilité microvasculaire des* vaisseaux endoneuraux du nerf tibial sur des lapins après une irradiation par 1 100 R de rayons de Roentgen correspondant à une LD_{50}. Cette technique de traçage n'a pas permis à elle seule de détecter les lésions dues à l'irradiation. L'addition d'un léger dommage ischémique, incapable par lui même de causer des troubles de la perméabilité, a cependant révélé une nette lésion vasculaire au cours des deux premières semaines après l'irradiation.

REFERENCES

ANGGÅRD E ARTURSON G and JONSSON C E Efflux of prostaglandins in lymph from scolded tissue (Abstract) Acta physiol scand 80 (1970) 46

ARTURSON G Personal cummunication 1970

— and THOREN L Capillary permeability following ionizing radiation p 83 *In* Combined injuries and shock Edited by B Schildt and L. Thoren Almqvist & Wiksell Stockholm 1968

BELFRAGE P and SCHILDT B Increased sensitivity to the muscle relaxing effect of succinyl choline Acta anaesth scand 11 (1967) 65

— — Muscle blood flow in whole body irradiated rabbits Res Inst Nat Def (Stockholm) Report C 1283—27 (1968)

BERGSTROM R Changes in peripheral nerve tissue after irradiation with high energy protons Acta radiol 58 (1962) 301

CHERNOV G A SHEREMFT Z I and LENSKAYA R Effect of irradiation on vascular permeability and on blood mucopolysaccharide and serotonin levels Fed Proc 24 (1965) 974

CRONKITE E P and BOND V P Radiation injury in man Charles C Thomas Springfield Illinois 1960

EFSKIND L Vaskulare Veranderungen nach intravenoser Injektion von Thoriumdioxyd (Thorotrast) Acta chir scand 84 (1940) 177

ELLINGER F Die biologischen Grundlagen der Strahlenbehandlung ein Lehrbuch für Studierende und Ärzte Sonderbande zur Strahlentherapie 20 (1935) 1

FURTH I ANDREWS G A STOREY R H and WISH L The effect of x irradiation on erythrogenesis plasma and cell volumes Sth med J (Bgham Ala) 44 (1951) 85

GROTTE G Passage of dextran molecules across capillary walls Acta chir scand (1956) Suppl No 211

LAZARUS-BARLOW W S On the histological and some other changes produced in animals by exposure to the gamma rays of radium Spec Rep Ser med Res Coun (Lond) No 62 (1922) 33

LINSER P Beitrag zur Histologie der Rontgenwirkung auf die normale menschliche Haut Fortschr Rontgenstr 8 (1905) 97

LUNDBORG G Ischemic nerve injury Experimental studies on intraneural microvascular pathophysiology and nerve function in a limb subjected to temporary circulatory arrest Scand J plast Reconstr Surg (1970) Suppl No 6

MELLICK R and CAVANAGH J B Longitudinal movement of radioiodinated albumin within extravascular spaces of peripheral nerves following three systems of experimental trauma J Neurol Neurosurg Psychiat 30 (1967) 458

OLSSON Y Studies on vascular permeability in peripheral nerves II Distribution of circulating fluorescent serum albumin in rat sciatic nerve after local injection of histamine 5 hydroxytryptamine and compound 48 80 Acta physiol scand 69 (1966) Suppl No 284

PAINTER E E PROSSER C L and MOORE M C Physiological observation on rabbits exposed to single doses of x rays USAEC (1947) Report MDDC-761

PORTER C A and WHITE C J Multiple carcinomata following chronic X ray dermatitis Ann Surg 46 (1907) 649

RHOADES R P The vascular system *In* Histopathology of irradiation from external and internal sources Edited by W Blom McGraw Hill Book Co New York 1948

RUBIN I and CASARETT G W Clinical radiation pathology W B Saunders Company Philadelphia London and Toronto 1968

SCHACHTER M Kallikreins and kinins Physiol Rev 49 (1969) 509

SCHILDT B and ARTURSON G Microvascular permeability following ionizing radiation Heiligenberg Conference August 3—4 1970
— och SCHILDT E Verkan av helkroppsbestrålning på kanin I LD_{50} bestamning av rontgenstrålning (In Swedish) Res Inst Nat Def (Stockholm) Report 1034 F173 (1963)
— and THORÉN L Experimental and clinical aspects of combined injuries *In* Combined injuries and shock Edited by B Schildt and L Thorén Almqvist & Wiksell Stockholm 1968
STEINWALL O and KLATZO J Double tracer methods in studies on blood brain barrier dysfunction and brain oedema Acta neurol scand 41 (1965) Suppl No 13
VÁRTERESZ V Pathophysiologie der Strahlenwirkung *In* Strahlenbiologie Herausgegeben von V Várterész Akadémiai Kiado Budapest 1966
WILHELM D L The mediation of increased vascular permeability in inflammation Pharmacol Rev 14 (1962) 251
WISH L FURTH J SHEPPARD C W and SHREY R H Disappearance rate of tagged substances from the circulation of roentgen irradiated animals Amer J Roentgenol 67 (1952) 628
WOLBACH S B A summary of effects of repeated roentgenray exposures upon the human skin antecedent to the formation of carcinoma Amer J Roentgenol 13 (1925) 139

FROM THE RESEARCH INSTITUTE OF NATIONAL DEFENCE SUNDBYBERG SWEDEN

RADIOSTRONTIUM INDUCED CARCINOMAS OF THE EXTERNAL EAR

by

AGNAR NILSSON

The frequencies of carcinomas induced in the mucous membranes of the nose and mouth in mice were investigated in a previous study (NILSSON 1968) in relation to the dose of ^{90}Sr administered In the same material a significant number of carcinomas were also observed in or around the external ear The present report deals with the origin development and frequency of these carcinomas

Material and Methods Four groups of CBA mice 75 days old were treated intraperitoneally with $^{90}Sr(NO_3)_2$ In addition a control group of 95 animals without ^{90}Sr treatment was used for a study of the natural incidence of tumours At intervals of 7 14 21 and 30 days after injection of ^{90}Sr and then at monthly intervals five mice from each group were selected at random and sacrificed until all mice in each series had been utilized The experimental conditions and the ^{90}Sr doses employed are recorded in Table 1

After the mice had been sacrificed their heads were divided along the median plane fixed in Susa's solution decalcified in formic acid dehydrated in alcohol and embedded in paraplast as earlier described (NILSSON 1968) The heads were serially sectioned in a sagittal plane through the cartilaginous and bony

Submitted for publication 16 June 1970

Table 1

Experimental conditions and doses employed

Dose of ^{90}Sr in μCi/g body weight	Total number of mice	Number of mice killed in groups of 5 every month	Duration of experiment in days	Number of animals dead before sacrifice
1.6	120*	65	300	50
0.8	121	75	360	46
0.4	122	95	480	27
0.2	120**	100	540	17
Control	95	94***	570	1

* Out of these animals five were lost during the experiment.
** Out of these animals three were lost during the experiment.
*** Only four animals were sacrificed in the last test group.

Table 2

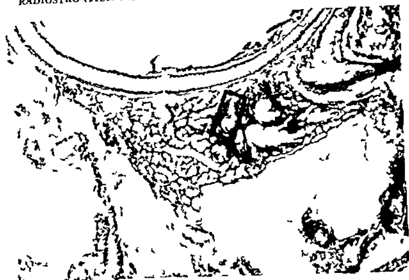
Frequency of ^{90}Sr induced carcinomas and precarcinomatous changes in the mucous membranes and sebaceous glands of left external ear

Dose of ^{90}Sr in μCi/g body weight	Mice with meta- and hyperplasia and slightly to moderately atypical nuclei		Mice with carcinomas	
	Number	Latency time	Number	Latency time
1.6	25	209.4 ± 12.0	18	257.7 ± 9.0
0.8	17	323.1 ± 9.7	2	324.5
0.4	3	484.5	0	—
0.2	0	—	0	—
Control	0	—	0	—

part of the left external auditory meatus and part of the middle ear. The section thickness was 5 μ and the equidistance between the sections 150 μ. All sections were stained according to the van Gieson method.

Results

Tumour frequencies and induction time. Twenty overt carcinomas were found, of which 18 in the 1.6 μCi and 2 in the 0.8 μCi group. Early changes of precarcinomatous type such as metaplasia and hyperplasia in combination with nuclear atypism were found in the 1.6, 0.8 and also 0.4 μCi groups, but



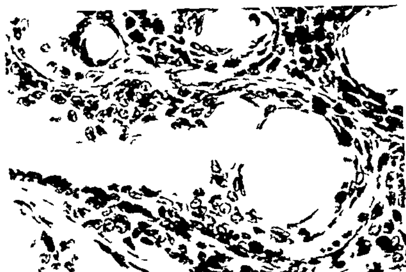


Fig 1 *Upper view* Sebaceous gland on the anterior external wall of the bony and cartilaginous part of the external auditory meatus from mouse 210 days after injection of 1 6 μCi ^{90}Sr/g body weight showing a circumscript area with distended excretory ducts and heavy accumulation of cells van Gieson ×50 *Lower view* Magnification of the inserted area Metaplasia and hyperplasia of cells inside glandular alveoli and ducts Moderate nuclear atypism van Gieson ×500



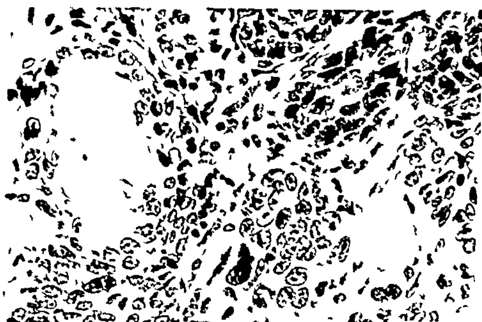


Fig. 2. *Upper view.* Carcinoma of sebaceous gland (A) on the anterior external wall of the auditory meatus. The gland and its orifice (B) into the external ear (C) is highly distended by accumulation of keratin. Mouse 240 days after injection of 1.6 μCi ^{90}Sr/g body weight. van Gieson ×50. *Lower view.* Magnification of carcinoma tissue from the inserted area. Van Gieson ×500.



Fig. 3. *Upper view.* Carcinoma of the sebaceous gland on the anterior wall of the auditory meatus. Mouse 270 days after injection of 1.6 μCi ^{90}Sr/g body weight. van Gieson ×30. *Lower view.* Magnification of carcinoma tissue from the inserted area. van Gieson ×500

not in the 0.2 μCi series. The latency times for these changes were significantly shorter with increasing dose (Table 2). The carcinomas were detected approximately 2 months earlier in the 1.6 than in the 0.8 μCi group. No carcinomas were detected in the control groups.

Site of tumour origin. These carcinomas originated predominantly from a sebaceous gland situated on the anterior outside wall of the external auditory meatus in close vicinity to bone and cartilage structures. From this gland an excretory duct lined with squamous epithelium passes into the external ear just at the border between the bony and cartilaginous part of the meatus. Nineteen out of the 20 cases of carcinomas found were located in this sebaceous gland. In some cases there was also a spread of the primary process to the mucous membrane of the external ear by infiltration through the excretory duct. Only one carcinoma primarily originating from the mucous membrane of the external ear was detected.

Tumour development and type of tumour. The earliest changes seem to start in this gland as a squamous cell metaplasia and hyperplasia of the epithelium of the smaller ductuli and glandular alveoli (Fig. 1), which successively become filled and distended by squamous cells. Inside these buds of proliferating squamous epithelium there was a successively increasing number of mitoses and of cells with atypical nuclei. In time these buds increased in size and acquired the characteristics of an overt squamous cell carcinoma invading most parts of the gland. Most of these carcinomas were highly differentiated keratin producing squamous cell carcinomas. In many of these the central part of the gland was filled with an accumulated mass of keratin, leaving only a narrow peripheral zone of compressed carcinoma tissue (Fig. 2), which, however, in time expanded into the gland in a protuberance-like manner (Fig. 3).

In many cases, instead of these changes, there was a more or less intense diffuse fibrosis in the gland.

Discussion

The results of this investigation have shown that squamous cell carcinomas can be induced by ^{90}Sr in or around the external ear in structures in close vicinity to bone. The overwhelming majority of these carcinomas originated from a sebaceous gland located on the anterior, bony wall of the external auditory meatus. On the average these carcinomas, like those of the mouth and nose earlier described

Table 3

Total number of carcinomas found at different sites of the head in relation to ^{90}Sr dose

Site	Dose of ^{90}Sr/g body weight							Total
	1 6 μC		0 8 μCi		0 4 μCi		0 2 μCi	
	Number	Induction time	Number	Induction time	Number	Induction time	Number	
Hard palat	34	235 1 ± 6 3	13	338 0 ± 7 5	0		0	47
Lower jaw	9	263 1 ± 6 1	2	352 5	2	443 5	0	13
Upper jaw	4	243 8	2	355 0	1	450	0	7
Mucous membranes of the nose	6	241 3 ± 7 9	4	321 8	0		0	10
Reg o olfactoria of the nose	3	250 0	0	—	0		0	3
Sebaceous ear gland	17	255 2 ± 9 5	2	324 5	0		0	19
Mucous membranes of the external ear	1	300	0	—	0		0	1
Total	34	248 5 ± 4 0	23	336 1 ± 5 5	3	446 8	0	100

(NILSSON 1968) seem to be induced at a considerable rate only after doses exceeding those which are considered optimal (0 7—1 0 μCi ^{90}Sr/g body weight FINKEL et coll 1958 NILSSON 1970 and others) for osteosarcomas Thus the total number of tumours was approximately 3 times greater in the 1 6 μCi than in the 0 8 μCi group and about 25 times greater than in the 0 4 μCi group (Table 3) The latency time was also considerably longer with decreasing dose As indicated in Table 3 the sites most prone to carcinoma development seem to be the mucous membranes of the hard palate and the sebaceous ear gland, at least in the 1 6 μCi group

SUMMARY

The effect of ^{90}Sr on the soft tissues of the external ear was studied at different intervals after an intraperitoneal injection of $^{90}Sr(NO_3)$ to four groups of mice Highly differentiated squamous cell carcinomas were detected in about 70 % of the mice given the highest dose of ^{90}Sr(1 6 μCi/g body weight) The majority of the carcinomas were found to start their development in a sebaceous gland outside the external auditory meatus

not in the 0 2 μCi series The latency times for these changes were significantly shorter with increasing dose (Table 2) The carcinomas were detected approximately 2 months earlier in the 1 6 than in the 0 8 μCi group No carcinomas were detected in the control groups

Site of tumour origin These carcinomas originated predominantly from a sebaceous gland situated on the anterior outside wall of the external auditory meatus in close vicinity to bone and cartilage structures From this gland an excretory duct lined with squamous epithelium passes into the external ear just at the border between the bony and cartilaginous part of the meatus Nineteen out of the 20 cases of carcinomas found were located in this sebaceous gland In some cases there was also a spread of the primary process to the mucous membrane of the external ear by infiltration through the excretory duct Only one carcinoma primarily originating from the mucous membrane of the external ear was detected

Tumour development and type of tumour The earliest changes seem to start in this gland as a squamous cell metaplasia and hyperplasia of the epithelium of the smaller ductuli and glandular alveoli (Fig 1), which successively become filled and distended by squamous cells Inside these buds of proliferating squamous epithelium there was a successively increasing number of mitoses and of cells with atypical nuclei In time these buds increased in size and acquired the characteristics of an overt squamous cell carcinoma invading most parts of the gland Most of these carcinomas were highly differentiated keratin producing squamous cell carcinomas In many of these the central part of the gland was filled with an accumulated mass of keratin, leaving only a narrow peripheral zone of compressed carcinoma tissue (Fig 2), which, however, in time expanded into the gland in a protuberance like manner (Fig 3)

In many cases, instead of these changes, there was a more or less intense diffuse fibrosis in the gland

Discussion

The results of this investigation have shown that squamous cell carcinomas can be induced by ^{90}Sr in or around the external ear in structures in close vicinity to bone The overwhelming majority of these carcinomas originated from a sebaceous gland located on the anterior, bony wall of the external auditory meatus On the average these carcinomas, like those of the mouth and nose earlier described

FROM THE DEPARTMENT OF RADIOLOGY, MEDICAL COLLEGE OF VIRGINIA, RICHMOND VIRGINIA U S A

RADIATION FOR IMMUNOSUPPRESSION IN HUMAN ORGAN TRANSPLANTATION

II Clinical experience

by

S H LEVITT R L ROYSTER F T O FOGHLUDHA J S WOLF, R R LOWER E R KING and L S DEGIORGI

At the Medical College of Virginia radiation therapy is used routinely after transplant of the donor kidney following the recommendations of KAUFFMAN et coll (1965) Using a high energy source 130 rad to the anterior surface of the kidney (calculated at 4 cm) is delivered on the first third fifth and seventh post transplant days The treatment field is outlined by silver clips placed at opposite poles of the kidney at the time of surgery In addition to the irradiation patients are also routinely placed on prednisone 5 to 60 mg and azothioprine 3 to 5 mg/kg A major problem of course in transplants is prevention of threatened rejection following the initial routine procedures

From the fall of 1962 until January 1 1970 a total of 140 patients have undergone kidney transplantation at our institution 81 of these (57 8 %) are living (Table 1) Of these patients 104 received a single transplanted kidney with irradiation being used as a primary immunosuppressive agent Table 2 reflects these results Patients receiving a kidney from a near relative all of whom

Submitted for publication 11 May 1970

ZUSAMMENFASSUNG

Es wurde die Wirkung von ^{90}Sr auf die weichen Gewebe des äusseren Ohres zu verschiedenen Zeitpunkten nach einer intraperitonealen Injektion von $^{90}Sr(NO_3)_2$ bei vier Gruppen von Mäusen untersucht. Hoch differenzierte squamöse Zell-Karzinome wurden in etwa 20% der Mäuse, denen die höchste Dosis von ^{90}Sr (1.6 μCi/g Körpergewicht) gegeben war, gefunden. Der Hauptteil der Karzinome begann seine Entwicklung von einer Talg-Drüse ausserhalb des äusseren Gehörganges.

RÉSUMÉ

L'auteur a étudié l'effet du ^{90}Sr sur les tissus mous de l'oreille externe à différents intervalles après une injection intrapéritonéale de $^{90}Sr(NO_3)_2$ à quatre groupes de souris. Il a trouvé des épithélioma très différenciés chez 20% environ des souris qui avaient reçu la plus forte dose de ^{90}Sr (1.6 μCi/g de poids corporel). Il a constaté que la plupart des épithélioma prenaient leur origine dans une glande sébacée en dehors du conduit auditif externe.

REFERENCES

FINKEL, M. P., BISKIS, B. O. and SCRIBNER, G. M.: The influence of strontium 90 upon life span and neoplasms of mice. Geneva Conference Paper (1958) 1/911.

NILSSON, A.: Pathologic effects of different doses of ^{90}Sr in mice. Development of carcinomas in the mucous membranes of the head. Acta radiol. Ther. Phys. Biol. 7 (1968), 27.

— Pathologic effects of different doses of ^{90}Sr in mice. Dose effect relationship in ^{90}Sr induced bone tumours. Acta radiol. Ther. Phys. Biol. 9 (1970), 155.

FROM THE DEPARTMENT OF RADIOLOGY, MEDICAL COLLEGE OF VIRGINIA, RICHMOND, VIRGINIA USA

RADIATION FOR IMMUNOSUPPRESSION IN HUMAN ORGAN TRANSPLANTATION

II Clinical experience

by

S H LEVITT R L ROYSTER F T O FOGHLUDHA J S WOLF, R R LOWER E R KING and L S DEGIORGI

At the Medical College of Virginia radiation therapy is used routinely after transplant of the donor kidney following the recommendations of KAUFFMAN et coll (1965) Using a high energy source 130 rad to the anterior surface of the kidney (calculated at 4 cm) is delivered on the first third fifth and seventh post transplant days The treatment field is outlined by silver clips placed at opposite poles of the kidney at the time of surgery In addition to the irradiation patients are also routinely placed on prednisone 5 to 60 mg and azothioprine 3 to 5 mg/kg A major problem of course in transplants is prevention of threatened rejection following the initial routine procedures

From the fall of 1962 until January 1 1970 a total of 140 patients have undergone kidney transplantation at our institution, 81 of these (57 8 %) are living (Table 1) Of these patients 104 received a single transplanted kidney with irradiation being used as a primary immunosuppressive agent Table 2 reflects these results Patients receiving a kidney from a near relative all of whom

Submitted for publication 11 May 1970

Table 1

Kidney transplants from August 1962 to January 1970

	Number of patients		Total
	Living	Dead	
Single transplants			
Relative	48 (64)	27	75
Nonrelative	0	3	3
Cadaver	21 (53 8 %)	18	39
Total	69 (58 9 %)	48	117
Multiple transplants (53 kidneys)	12 (52 2 %)	11	23
Total number of transplants	81 (57 8 %)	59	140

were siblings or parents of the patient, had better survival than those who received either a nonrelative's kidney or a cadaver kidney Twenty two (58 %) of the 38 patients receiving single cadaver kidneys survived over one year and 46 of 66 (70 %) of single relative transplants have survived one year

Thirty five of the 104 single transplant patients, including 11 patients receiving cadaver kidneys, required only the initial course of 600 rad irradiation and are without evidence of rejection Eight of these 35 are dead of this date, but the deaths were not related to kidney rejection (Table 3) The success rate using 600 rad was 24/66 (36 %) for relative kidneys and 11/38 (29 %) for cadaver kidneys

Rejection is one of the major complications of organ transplantation Clinically there is fever, swelling and tenderness of the transplant, mild anorexia, and decreased urinary output Laboratory findings are multitudinous, including lymphocytes in the urine and blood serum lactic dehydrogenase (LDH) changes, depression of the C fraction of the complement

The most useful daily indices for the detection of threatened rejection are the sudden appearance of oliguria, associated with a rise in blood urea nitrogen (BUN), with or without fever Sometimes the BUN will increase without concurrent rise in creatine but the more severe crises are usually associated with elevation in the serum creatine and a fall in creatine clearances

The primary treatment of threatened kidney rejection is prednisone (up to 400 mg daily) and actinomycin D (200 to 400 mg daily for 3 to 4 days) If the impending rejection fails to respond to these initial measures, local irradiation to the graft is then utilized Doses of 150 rad are given daily up to 1 500 rad if

Table 2

Patients with a single transplant receiving irradiation to the kidney only as adjuvant immunosuppression

Donor source	Total	Living	Dead	Survival				
				1 year	2 years	3 years	4 years	5 years
Relative	66	46 (70%)	20	46 (70%)	40 (60%)	33 (50%)	24 (36%)	1 (21%)
Nonrelative	0	0	0					
Cadaver	38	21 (55%)	17	22 (58%)	15 (39%)	11 (29%)	5 (13%)	1 (2 %)
Total	104	67	37					

Table 3

Patients with a single transplant receiving 600 rad to the kidney and with no evidence of rejection

Donor source	Total	Living	Dead	Survival				
				1 year	2 years	3 years	4 years	5 years
Relative	24	21	3	19	19	18	12	7
Nonrelative	0	0	0					
Cadaver	11	6	5	6	4	3	1	0
Total	35	27	8					

One patient also received antilymphocyte serum

Cause of death not related to kidney rejection (sepsis, myocardial infarction, auto accident, etc.)

Table 4

Single transplant patients who required additional radiation immunosuppression for threatened rejection after initial irradiation — The retreatments were all given to single allografts and this data does not include patients who received more than one kidney

Number of treatments	Number of cases	Average time from first to last irradiation (weeks)	Living	Dead	Average survival (months)
1	22	7.8	19	3	34.6
2	16	11.4	13	3	30.7
3	14	18.8	7	7	25.8
4	6	30.7	3	3	23.2
5	5	13.4	0	5	9.2
6	2	22.0	0	2	8.5

Table 1

Kidney transplants from August 1962 to January 1970

	Number of patients		Total
	Living	Dead	
Single transplants			
Relative	48 (64 %)	27	75
Nonrelative	0	3	3
Cadaver	21 (53 8)	18	39
Total	69 (58 9 %)	48	117
Multiple transplants (53 kidneys)	12 (52 2)	11	23
Total number of transplants	81 (57 8 %)	59	140

were siblings or parents of the patient, had better survival than those who received either a nonrelative's kidney or a cadaver kidney Twenty two (58 %) of the 38 patients receiving single cadaver kidneys survived over one year and 46 of 66 (70 %) of single relative transplants have survived one year

Thirty five of the 104 single transplant patients, including 11 patients receiving cadaver kidneys, required only the initial course of 600 rad irradiation and are without evidence of rejection Eight of these 35 are dead of this date, but the deaths were not related to kidney rejection (Table 3) The success rate using 600 rad was 24/66 (36 %) for relative kidneys and 11/38 (29 %) for cadaver kidneys

Rejection is one of the major complications of organ transplantation Clinically there is fever, swelling and tenderness of the transplant, mild anorexia and de*creased urinary output Laboratory findings are multitudinous, including* lymphocytes in the urine and blood serum lactic dehydrogenase (LDH) changes, depression of the C" fraction of the complement

The most useful daily indices for the detection of threatened rejection are the sudden appearance of oliguria associated with a rise in blood urea nitrogen (BUN), with or without fever Sometimes the BUN will increase without concurrent rise in creatine, but the more severe crises are usually associated with elevation in the serum creatine and a fall in creatine clearances

The primary treatment of threatened kidney rejection is prednisone (up to 400 mg daily) and actinomycin D (200 to 400 mg daily for 3 to 4 days) If the impending rejection fails to respond to these initial measures, local irradiation to the graft is then utilized Doses of 150 rad are given daily up to 1 500 rad if

Table 6

Total body irradiation as primary immunosuppression

Year	Patient	Age (years)	Donor	Living	Dead	Dose in R	Survival
1963	E A	28	Relative		—	150	1 mo
1962	G B	25	Cadaver	—		150	7 yrs 2 mo
1962	J C	15	Relative		—	300	1 mo
1962	M D	19	Relative	—		150	7 yrs 1 mo

Received 150 R to spleen as well

Received 200 R to transplanted kidney second kidney transplanted in April 1964 and 600 R given to kidney

Received 400 R to kidney as well

Received 150 R to spleen and 100 R to kidney in November 1962 150 R to kidney in March 1966 and 300 R in January 1967 had second and third transplants in May 1967 and received 600 R to kidney in May 1967 had fourth transplant in September 1967 and received 1 200 R to this kidney

Twenty three patients received more than one kidney due to rejection of previous allografts Two patients received 4 kidneys and one is still alive

Twenty-one of the 23 patients with a second or more kidney allograft received the graft from a cadaver Nine of these multiple transplant patients have good renal function at the time of this report 11 have died and 3 rejected their most recent cadaver transplant and are being maintained on dialysis A total of 38 cadaver renal allografts were used in maintaining these 23 patients (Table 5)

The first 4 patients transplanted in late 1962 and early 1963 received total body irradiation prior to the transplant These patients are listed in Table 6 The first patient J C received 300 R measured in air to the midline axis of her body in one exposure She died after slightly less than one month her death complicated by evidence of marked bone marrow depression which was attributed to the total body irradiation The next 3 patients received 150 R of total body irradiation Two of these (G B and M D) still survive G B received an initial graft from a cadaver and M D has received three successive cadaver kidneys after rejection of her mother s kidney

A group of patients in 1963 and early 1964 received irradiation to their spleen in addition to the kidney irradiation This was performed in an attempt to improve control of the immune response by the host against the transplanted kidney It was believed that by irradiating the spleen of the recipients the afferent and efferent arcs of the immune response could be suppressed and that survival

Table 5

Duration of graft survival of multiple kidney transplants

Patient	Number of transplants and donor				Transplant survival			
	First	Second	Third	Fourth	First	Second	Third	Fourth
R A	Relative	Cadaver			40 mo	12 mo		
H B	Cadaver	Relative			2 5 mo	[1]24 mo		
G B	Cadaver	Relative			16 mo	[1]68 mo		
H B	Cadaver	Cadaver			11 mo	[2] 3 mo		
R B	Cadaver	Cadaver			10 mo	[2] 1 day		
J C	Nonrelative	Cadaver			2 mo	[2]57 mo		
B C	Relative	Cadaver			13 mo	[2] 4 mo		
M D	Relative	Cadaver	Cadaver	Cadaver	51 mo	[2] 0 mo	2 mo	[illegible]1 mo
K F	Cadaver	Cadaver			6 days	64 mo		
S C	Cadaver	Cadaver			3 days	[2] 2 mo		
L H	Cadaver	Cadaver			5 mo	[2] 8 mo		
P H	Relative	Cadaver	Cadaver		15 mo	[1] 3 mo	57 mo	
W J	Relative	Cadaver			2 mo	[2] 0 mo		
C N	Relative	Cadaver			27 mo	[1]44 mo		
D P	Cadaver	Cadaver			6 mo	10 mo		
M P	Relative	Cadaver			31 mo	[1]14 mo		
K R	Cadaver	Cadaver	Cadaver		2 mo	1 mo	[4]2 mo	
R R	Relative	Cadaver			25 mo	11 days		
L R	Relative	Cadaver	Cadaver		15 mo	13 mo	7 days	
S S	Relative	Cadaver	Cadaver		8 mo	2 mo	[4]0 mo	
C S	Relative	Cadaver			12 days	9 mo		
H S	Cadaver	Cadaver			12 days	40 mo		
P S	Relative	Cadaver	Cadaver	Cadaver	0 mo	2 mo	1 5 mo	[2]18 days

[1] Living with good renal function at present
[2] Patient deceased
Rejected kidney on day of transplant
[4] Rejected last kidney on dialysis

necessary Each patient is evaluated utilizing clinical and laboratory data daily to determine the necessity for further irradiation The results of repeat irradiation for the single kidney transplants are given in Table 4 It should be noted that the greater the number of treatments received by the patients, the less chance for success This could be explained on the basis that the additional radiation was necessary because of continued rejection of the grafted kidney Of the 65 patients receiving additional radiation attempting to reverse the rejection phenomena, 42 are living and 23 are deceased

Table 8

Patients receiving irradiation to transplanted kidney plus ^{90}Sr shunt extracorporeal irradiation and antilymphocyte serum (ALS)

Patient	Donor	Number of transplants	Living	Dead	Period when ALS given: Acute rejection <4 months	Period when ALS given: Chronic rejection >4 months	Survival
H B	Cadaver×2	2		—	—		23 months
R C	Relative	1		—	—	—	6 months
S G	Cadaver×2	2		—	—		12 months
L H	Cadaver×2	2		—	—	—	14 months
E R	Relative and cadaver ×2	3		—	—	—	45 months
S S	Relative and cadaver×2	3	—			—	41 months
P S	Relative and cadaver ×3	4		—	—		25 months

Received shunt for acute rejection of first and second kidneys
Received shunt for acute rejection of second kidney
Received shunt for acute and chronic rejection of first kidney only
Received shunt for chronic rejection of first kidney and acute rejection of second kidney
Received shunt for chronic rejection of first kidney

formation as of January 1 1968 (1 741 renal transplants) That report divided transplants as prior to January 1966, and after that date and evaluated the results accordingly It was pointed out in that report that the host s acceptance of fresh cadaver kidney transplants had greatly improved in the past several months compared with experience prior to January 1966 probably as a result of better pre transplant organ preservation and better methods of immunosuppression There had been little improvement in the parent kidney host s acceptance but a moderate amount of improvement in the sibling kidney host s acceptance was noted This latter improvement was probably on the basis af perfecting methods of immunosuppression as well as the development of tissue typing techniques It should be pointed out however, that in our experience tissue typing has not significantly improved transplant 1 year survival as evaluated at this time (Table 11) Finally we have evaluated the 5 year survival in our kidney transplants of the 52 patients transplanted during the period August 1962 to June 1964 22 are living (5 of these have had multiple transplants) and 30 are deceased The 5 year survival (through December 1969) was 42 3 %

Table 7

Irradiation of kidney and spleen as primary immunosuppression

Year	Patient	Age (years)	Donor	Living	Dead	Dose in R		Survival
						Kidney	Spleen	
1963	J B	20	Relative		—	750	150	5 mo
1963	B B	18	Nonrelative		—	600	150	2 mo
1963	D B	44	Nonrelative		—	900	1 050	3 weeks
1964	J C	10	Relative	—		750	150	5 yrs 6 mo
1963	S G	23	Relative		—	1 050	150	3 mo
1963	H H	37	Nonrelative		—	1 050	150	3 weeks
1963	P H [1]	11	Relative	—		1 050	150	6 yrs 9 mo
1964	W L	17	Relative	—		1 050	150	5 yrs 7 mo
1963	R R	35	Relative		—	1 100	150	4 mo
1963	C S	30	Relative		—	600	150	
1963	C S	30	Cadaver			900	150	11 mo
1964	R S	29	Cadaver		—	1 050	150	3 yrs 7 mo
1963	J W	15	Relative	—		600	150	6 yrs 7 mo
1963	A W	22	Relative		—	750	150	5 mo

[1] Has since had second and third kidney transplants

might be improved The early results did not substantiate this theory and the technique was abandoned in 1964 (Table 7)

Extracorporeal irradiation was first used in 1965 in patients undergoing rejection (Table 8) It has been used in a total of 7 patients to date Six of these patients are deceased and one is living

Antilymphocyte serum (ALS) was administered to 11 patients, who were undergoing rejection (Table 9) Five patients are still living with their first transplants for periods ranging from 19 months to 26 months

This series of patients treated with routine irradiation post transplant and irradiation for rejection crises is the largest group of kidney transplants treated in this manner The majority of kidney transplant patients in other centers do not receive irradiation at any time

The results of cadaver transplants at our institution using irradiation are superior to those of other centers not using irradiation, but other factors such as operative technique, methods of preservation, are also important in determining success of the transplant procedure

Table 10, from the Sixth Report of the Human Kidney Transplant Registry, presents a summary of the results of all the accumulated kidney transplant in

Table 10

Cumulative kidney transplant survival to January 1968 — (From Kidney graft survival rate improving J Amer med Ass 206 (1968) [illegible]5)

Donor	Number of transplants	Survival (per cent)	
		1 year	2 years
Monozygotic twin	4[illegible]	90	88
Dizygotic twin	14	79	51
Sibling	28[illegible]	68	63
Parent	4[illegible]	6[illegible]	54
Other blood relative	34	61	61
Living unrelated	151	23	19
Cadaver	760	35	26
Total	1 741		

Table 11

Comparison of 1 year survival before and after the introduction of tissue typing

	Donor		Total	Number surviving one or more years
	Relative	Cadaver		
Patients transplanted in 1966 before tissue typing	14	10	24	19 (79.2 [illegible])
Patients transplanted June 1967 to May 1968 after tissue typing	12	6	18	13 (72.2 [illegible])

Our first patient was treated with the alternate day treatment technique utilizing [illegible]Co (80 cm FSD 15 cm × 15 cm anterior thoracic field) commencing with the first post transplant day He only received 3 treatments of 150 rad surface dose each (100 rad each to the graft calculated at 10 cm) prior to rejecting on the seventh post transplant day It is now felt that his dose of antilymphocyte serum and steroids was not sufficient In addition, the radiation dose was not equivalent to the dose used on the kidney since we were calculating maximum dose and not depth dose and this was not sufficient to help prevent rejection

Since then 4 more transplants have been done One was not treated with irradiation and rejected One was treated intermittently with 3 treatments 150 rad depth dose (through a 15 cm × 15 cm anterior thoracic port) each on non consecutive days for two rejection episodes and rejected on the second episode

Table 9

Patients receiving irradiation to transplanted kidney and antilymphocyte serum (ALS)

Patient	Donor	Number of transplants	Living	Dead	Period when ALS given: Acute rejection <4 months	Chronic rejection >4 months	Survival
R A [1]	Relative and cadaver	2	—		—		54 months
M A	Cadaver	1		—	—		3 months
L B [2]	Cadaver	1	—		—	—	26 months
B C [1]	Relative and cadaver	2		—	—		19 months
M D [2]	Relative and cadaver × 3	4	—		—		85 months
W F [2]	Cadaver	1	—		—		20 months
H F [2]	Cadaver	1	—		—		19 months
C J [2]	Cadaver	1	—		—		26 months
F J	Relative	1	—			—	19 months
M P [4]	Relative and cadaver	2	—			—	47 months
P S [5]	Relative and cadaver 3	4		—	—		25 months

[1] ALS given for acute rejection of second kidney only
[2] ALS given on day of transplant
[3] ALS given for chronic rejection of first kidney only
[4] ALS given on day of transplant of third and fourth kidneys
[5] ALS given for acute rejection of fourth kidney only

Insofar as heart transplantations are concerned, no definite regimen for initial immunosuppression of prevention of rejection has been developed in the 5 heart transplants that have been carried out at this institution The most important immunosuppressive agents are antilymphocyte serum immuran and prednisone with radiation an adjunct Rejection here is of course a major problem and is characterized clinically first by a precordial friction rub and then progressive congestive failure and by a fall in voltage and arrhythmia Because of the possibility that fluid accumulation in the pericardium may be the cause of the low voltage, ECG changes from a myocardial electrode are felt to be more reliable Current studies are underway to utilize enzyme changes Preliminary investigation seems to demonstrate that elevations in bands I and II of the LDH (lactic dehydrogenase) isozyme and band I of the CPK (creatine phosphate kinase) isozyme may afford help in the detection of rejection crisis

SUMMARY

The human kidney and heart transplants performed at the Medical College of Virginia since 1962 are discussed. Out of 140 patients with kidney transplants 81 survived and of 5 heart transplants 1 survived. Kidney transplants are routinely treated with irradiation post operatively to the graft site and receive further irradiation for rejection crises. Irradiation to cardiac transplants is used for rejection. Results of irradiation and other agents used in immunosuppression in the treatment of heart and kidney transplant rejections are discussed.

ZUSAMMENFASSUNG

Die menschlichen Nieren- und Herztransplantationen, die seit 1962 an der Medizinischen Hochschule von Virginia ausgeführt worden sind, werden besprochen. Von 140 Patienten mit Nierentransplantation haben 81 und von 5 Patienten mit Herztransplantation einer überlebt. Nierentransplantierte werden routinemässig postoperativ durch Bestrahlung der Transplantationsseite behandelt und erhalten weitere Bestrahlung bei Abstossungs-Krisen. Bestrahlung von Herztransplantierten wird bei einer Abstossung verwendet. Ergebnisse von Bestrahlung und anderen Mitteln, die zur Unterdruckung der Immunität bei der Behandlung der Abstossung von Herz- und Nierentransplantaten verwendet werden, sind besprochen.

RÉSUMÉ

Les auteurs étudient les greffes de rein et de cœur humains effectuées au Medical College de Virginie depuis 1962. Sur 140 sujets ayant subi une greffe de rein, 81 ont survécu et sur 5 sujets ayant subi une greffe de cœur, un a survécu. Les greffes de rein sont traitées de façon habituelle par une irradiation postopératoire du siège de la greffe et subissent une autre irradiation pour les crises de rejet. L'irradiation des greffes cardiaques est utilisée en cas de rejet. Les auteurs examinent les résultats de l'irradiation et des autres agents utilisés pour l'immuno-suppression dans le traitement du rejet des greffes de cœur et de rein.

REFERENCES

BANKS D E, AUBURN R F, HUBAY C A and PERSKY L. Effects of intermittent irradiation in sites on renal homotransplantation. J Urol 86 (1961) 181

CONVERSE J M and CASSON P R. The historical background of transplantation. *In* Human transplantation. First edition, p 3. Grune and Stratton, New York 1968

CRONKITE E P and CHANANA A D. Ionizing radiation. *In* Human transplantation. First edition, p 423. Grune and Stratton, New York 1968

GOOD R A, GABRIELSEN A E, PETERSEN R D A et coll. The development of the central and peripheral lymphoid tissue. Autogenetic and phylogenetic consideration. The Thymus. Experimental and Clinical Studies. CIBA Foundation Symposium. Little, Brown and Company, Boston 1966

GOWANS J L. The role of lymphocytes in the destruction of homografts. Brit med Bul 21 (1965) 106

GRAHAM W H, CHILDS J W, DEGIORGI L S et coll. The effect of local graft irradiation on reject on of canine cardiac allografts. J thorac cardiovasc Surg 60 (1970) 730

HUME D M. Personal communication (1968)

One patient was successfully treated with irradiation, increased prednisone, and antilymphocyte serum He received 2 treatments of 150 rad (at 13 cm depth through a 15 cm × 15 cm anterior thoracic port) on alternate days at the time of his second rejection which occurred two months after transplant He had a good response with reversal of the bundle branch block that had developed and is doing well now more than one year after the rejection and the transplant Our 5th heart transplant patient was treated on the 9th and 10th days post transplant because of threatened rejection as evidenced by lethargy, fatigue and a peri cardial rub, a gallop rhythm and decreased voltage on ECG He received 300 rad twice each day delivered through anterior and posterior 14 cm × 14 cm thoracic fields He responded to this treatment in addition to other agents used Approximately one month later he suffered another rejection crises and despite 2 more radiation treatments in addition to other immunosuppressive agents, he expired due to rejection Despite this outcome this experience seems to confirm our findings in the dog heart transplant experiments that doses of 300 rad are more effective than lower doses in ameliorating the rejection

Conclusion

Radiation has been used clinically as a method of immunosuppression in kidney transplants as total body irradiation, locally to transplanted kidney, and extracorporeally to the circulating blood Because of high mortality of total body radiation, it has been abandoned in clinical practice Local graft irradiation has been used successfully clinically in transplantation of the kidney and the heart At our institution, it is used sequentially in the early kidney transplant period and is also used during periods of accelerated rejection Experimental data supports its effectiveness as an immunosuppressive agent Extracorporeal radiation of the circulating blood has also been shown experimentally to be an effective im munosuppressant Its limited use thus far in man has shown that it is effective in reversing some episodes of accelerated rejection but there is no effect on chronic rejection Both of the latter methods of radiation serve as a useful adjunct to the basic immunosuppression armamentarium of the transplant Thus far in the 5 human heart transplants at this institution, radiation has been used suc cessfully in only two patients and this was for threatened rejection after a suc cessful transplant In future human heart allotransplants we would continue to use radiation in higher doses than we had before and earlier in the cour e of treatment

It must be emphasized that radiation is a complementary method of im munosuppression in organ transplant and cannot sustain prolonged allogenic transplant survival when used alone

SUMMARY

The human kidney and heart transplants performed at the Medical College of Virginia since 1962 are discussed Out of 140 patients with kidney transplants 81 survived and of 5 heart transplants 1 survived Kidney transplants are routinely treated with irradiation post operatively to the graft site and receive further irradiation for rejection crises Irradiation to cardiac transplants is used for rejection Results of irradiation and other agents used in immunosuppression in the treatment of heart and kidney tran plant rejections are discussed

ZUSAMMENFASSUNG

Die menschlichen Nieren und Herztransplantationen die seit 1962 an der Medizinischen Hochschule von Virginia ausgeführt worden sind werden besprochen Von 140 Patienten mit Nierentransplantation haben 81 und von 5 Patienten mit Herztransplantation einer uberlebt Nierentransplantierte werden routinemassig postoperativ durch Bestrahlung der Transplantationsseite behandelt und erhalten weitere Bestrahlung bei Abstossungs Krisen Bestrahlung von Herztransplantierten wird bei einer Abstossung verwendet Ergebnisse von Bestrahlung und anderen Mitteln die zur Unterdruckung der Immunitat bei der Behandlung der Abstossung von Herz und Nierentransplantaten verwendet werden sind besprochen

RÉSUMÉ

Les auteurs etudient les greffes de rein et de cœur humains effectuees au Medical College de Virginie depuis 1962 Sur 140 sujets ayant subi une greffe de rein 81 ont survecu et sur 5 sujets ayant subi une greffe de cœur un a survecu Les greffes de rein sont traitees de façon habituelle par une irradiation postopératoire du siege de la greffe et subissent une autr irradiation pour les crises de rejet L irradiation des greffes cardiaques est utilisee en cas de rejet Les auteurs examinent les resultats de l irradiation et d s autres agents utilises pour l immuno suppression dans le traitement du rejet des greffes de cœur et de rein

REFERENCES

BANKS D E AUBURN R F HUBAY C A and PERSKY L Effects of intermittent irradiation in sites on renal homotransplantation J Urol 86 (1961) 181

CONVERSE J M and CASSON P R The historical background of transplantation *In* Human transplantation First edition p 3 Grune and Stratton New York 1968

CRONKITE E P and CHANANA A D Ionizing radiation *In* Human transplantation First edition p 423 Grune and Stratton New York 1968

GOOD R A GABRIELSEN A E PETERSEN R D A et coll The development of the central and peripheral lymphoid tissue Autogenetic and phylogenetic consideration The Thymus Experimental and Clinical Studies CIBA Foundation Symposium Little Brown and Company Boston 1966

GOWANS J L The role of lymphocytes in the destruction of homografts Brit med Bul 21 (1965) 106

GRAHAM W H CHILDS J W DEGIORGI L S et coll The effect of local graft irradiation on rejection of canine cardiac allografts J thorac cardiovasc Surg 60 (1970) 730

HUME D M Personal communication (1968)

— Macie J. H., Kauffman Jr H. M. et coll. *Renal homotransplantation in man in modified recipients.* Ann. Surg. 158 (1963) 608.

— and Wolf J. S. Modification of renal homograft rejection by irradiation. Transplantation 5 (1967) 1175.

Kauffman H. M., Cleveland R. J., Dwyer J. J. et coll. Prolongation of renal homograft function by local graft radiation. Surg. Gynec. Obstet. 120 (1965) 39.

Kidney graft survival rate improving. J. Amer. med. Ass. 206 (1968) 25.

Loutit J. F. Lymphocytes, the Mackenzie lecture. Brit. J. Radiol. 36 (1963) 785.

Lower R. R., Kontos H. A., Kosek J. C. et coll. Experience in heart transplantation. Amer. J. Cardiol. 22 (1968) 766.

Micklem H. S. and Loutit J. F. Tissue grafting and radiation. Academic Press, New York 1966.

O'Lochlaudha I. I. Personal communication (1969).

— and Wolf J. S. Beta ray extracorporeal irradiators affording complete patient mobility. Radiology 90 (1968) 371.

Williams G. M., Hume D. M., Hudson R. P. et coll. Hyperacute renal homograft rejection in man. New Engl. J. Med. 279 (1968) 611.

Wolf J. S., McGavic J. D. and Hume D. M. Inhibition of the effector mechanism of transplant immunity by local graft irradiation. Surg. Gynec. Obstet. 122 (1966) 584.

— O'Lochlaudha I. I., Kauffman H. M. and Hume D. M. Prolongation of renal homograft survival by indwelling beta irradiation. Surg. Gynec. Obstet. 122 (1966) 1262.

Woodruff M. F. A., Robson J. S., Nolan B. et coll. *Homotransplantation of kidney in patients treated by preoperative local irradiation and postoperative administration of an antimetabolic immuno.* Report of six cases. Lancet 1963, II, p. 675.

FROM THE DEPARTMENT OF RADIOLOGY MEDICAL SCHOOL UNIVERSITY OF FLORENCE ITALY

INTESTINAL ABSORPTION OF RADIOIODINE LABELLED HUMAN SERUM ALBUMIN, MONO IODOTYROSINE AND DI IODOTYROSINE FOLLOWING ABDOMINAL RADIATION THERAPY

by

L CIONINI A BECCIOLINI L DALLA PALMA and G DE GIULI

Research has been carried out for the last ten years on the intestinal damage induced by irradiation of the lower abdomen in the course of radiation therapy of tumours not involving the gastro-intestinal tract This has included investigations of anatomic changes by conventional histologic methods electron microscopy and histochemistry (DE GIULI et coll 1965, DE DOMINICIS & GRECHI 1966)

Functional changes were investigated by determining the absorption of fatty acids neutral fats iron vitamin B_1 xylose glucose sucrose intestinal loss of macromolecules and biliary and pancreatic secretions (DE GIULI et coll 1965 GIANNARDI et coll 1965 DALLA PALMA et coll 1965 DALLA PALMA 1968) Morphologic changes in the intestinal loops not included in the field of irradiation have also been described (DE DOMINICIS & GRECHI 1965) All our previous and present work has been done in patients without signs of anatomic or

Submitted for publication 29 May 1970

Table 1

Results of previous investigations of intestinal absorption damage induced by abdominal irradiation

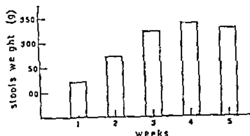
Substance	Treatment			No of patients
	Before	Halfway	End	
Absorption (mean %)				
Oleic acid	88 26	80 87	78 38	24
Triolein	89 04	69 93	64 25	21
Iron	39 11	10 94	28 19	18
Vitamin B_{12}	51 10	33 00	36 00	20
Maximum blood level (mean %)				
Glucose	55 40	41 60	37 40	50
Sucrose	61 70	39 10	36 90	22
Faecal loss (mean %)				
PVP	0 52	0 77	1 10	14
Urinary excretion (mean g/5 hrs)				
D Xylose	6 30	4 30	4 [illegible]0	28

functional conditions in the digestive tract before treatment The tests were carried out at least twice, more often three times, in each individual patient, before, halfway through and at the end of treatment

Table 1 gives the conclusive data obtained in previous work on the radiation induced malabsorption of investigated substances The variations in the weight of stools during treatment are indicated in the Figure

Material and Method Protein intestinal absorption in the present series was investigated in a group of female patients with tumours of the uterus admitted for radiation therapy after total hysterectomy and bilateral oophorectomy The technical data of the treatment (Cobalt 60) have been reported in a previous paper (De Giuli et coll 1965)

The early stage of the investigations was limited to an evaluation of the absorption of ^{131}I labelled human serum albumin (RISA) later, mono iodotyrosine (MIT) and di iodotyrosine *(DIT) absorption were also followed* Each of these iodinated aminoacids was administered to two different groups of patients at the same time as albumin, using two radioactive isotopes of iodine ^{131}I in the case of MIT and ^{1} I for labelling DIT The RISA in the investigation was labelled on tyrosine either with ^{1} *I or with* ^{131}*I depending on whether* the aminoacid administered at the same time was labelled with ^{131}I (MIT) or with ^{1} I (DIT) All the tracers were provided by the *Radiochemical Centre* Amersham, England The extent of the spontaneous degradation of the labelled compounds was tested before use by *paper chromatography*



Daily weight of stools (average values) in the five weeks during therapeutic treatment to the abdomen

The patients were given twenty drops of Lugol solution three times a day during the three days before the test in order to prevent thyroid uptake Fifty μCi of each tracer were administered to the fasting patient together with a high protein diet consisting of 120 g of ricotta (a type of cottage cheese) with a protein content of about 14 g Food was withheld for at least three hours following the administration of the labelled dose

During the following four days the stools were collected the patients evacuating carefully excluding urine directly in one litre plastic containers The stools were brought to constant volume with water and homogenized by means of an electric mixer to obtain uniform distribution of radioactivity before the latter was measured The containers in reproducible geometry, were placed in contact with a scintillator connected with a multichannel pulse analyser which allowed the discrimination of the photoelectric peaks of the two iodine isotopes employed The excreted fraction was evaluated by comparison with a sample prepared at the same time as the dose and containing a known quantity of the same The tests were carried out on each patient before halfway through (2 500 to 3 000 R) and at the end (5 000 R) of the treatment

MIT was chosen because its use would demonstrate any impairment of enzymatic hydrolysis since the albumin is labelled on tyrosine DIT was selected because it might be indicative of the part of the absorption occurring by simple diffusion

Results

The results relating to the absorption of the three substances investigated are reported separately and then compared where both were administered Table 2 gives the individual results as well as the condition of the abdomen during the period when the absorption test was being carried out Three different types of reaction are represented schematically in Table 3 in which the number of patients with each type of reaction is indicated for the three substances No explanation for the differences in the behaviour can be offered at this stage

Table 2

*Absorption of RISA, MIT or DIT expressed as a percentage of the administered dose — The eight patients with initial absorption values of RISA below 94 per cent are indicated by**

Case	RISA			MIT			DIT			Diarrhoea	
	Before	Half way	End	Before	Half way	End	Before	Half way	End	Halfway	End
1	95.9	94.8	92.1							+ − −	+ + −
2	95.1	93.6	93.7							+ + −	+ + +
3	95.0	95.0	92.9							+ + −	+ + −
4	94.5	93.6	93.7							+ + +	+ + +
5	96.7	92.7	86.8							+ + −	+ + −
6	97.6	92.4	70.7							+ − −	+ + +
7	98.3	95.3	93.8							+ + −	+ + −
8	96.8	93.0	92.3							+ + +	+ + −
9	95.2	67.0	89.0							− − −	− − −
10	96.6	93.4	99.1							+ + −	+ − −
11	98.3	95.3	93.8							+ + −	+ + −
12	94.5	89.5	89.5							+ + −	+ + −
13	96.8	85.2	90.3							− − −	− − −
14	96.2	95.5	95.8	92.6	90.0	85.7				+ − −	+ + −
15	96.6	83.2	93.3	82.8	78.7	90.9				− − −	− − −
16	97.9	85.2	94.2	95.4	86.5	92.8				+ + −	+ + −
17	94.0	94.4	90.9	93.0	70.2	94.7				+ + −	− − −
18	98.0	91.0	97.4	97.2	91.7	87.9				− − −	− − −
19	94.4	91.3	91.7	95.3	85.1	80.9				+ − −	− − −
20	98.2	96.1	95.5	92.0	95.8	81.7				− − −	− − −
21	99.6	97.8	91.2	98.5	97.4	90.3				− − −	− − −
22	99.2	79.3	96.2	99.3	87.0	94.6				− − −	− − −
23	94.4	92.2	98.5	92.1	92.4	98.2				− − −	+ − −
24	96.1	95.0	93.5	96.0	95.0	93.8				+ + −	+ − −
25	96.3	87.5	93.9	93.7	90.8	94.1				− − −	− − −
26	96.2	88.6	96.2	92.6	85.3	93.1				+ − −	+ − −
27	94.9	88.2	92.2	94.2	93.1	88.0				− − −	− − −
28	99.9	94.6	93.7	98.7	92.8	98.4				+ + −	+ − −
29	99.0	96.3	90.0	99.0	92.4	98.0				− − −	− − −
30	99.0	99.0	99.8	99.0	99.0	98.0				− − −	− − −
31	97.7	97.4	98.1	95.0	95.5	94.0				− − −	− − −
32	94.2	91.5	95.1	90.8	89.5	99.3				+ + −	+ + −
33	99.0	91.2	97.8	97.8	94.3	92.0				+ − −	− − −
34	95.4	92.0	81.8				87.5	82.1	56.7	+ + −	+ − −
35	95.3	88.0	78.3				92.9	77.2	59.2	+ − −	+ + −
36	97.1	91.3	89.7				95.0	75.9	62.2	+ + −	+ − −
37	95.6	77.4	75.8				91.2	73.7	57.3	+ − −	+ + −
38	96.4	91.4	90.4				96.3	76.6	73.7	− − −	− − −
39	97.5	87.4	88.8				91.5	91.5	76.4	+ + +	+ + −

Table 2 (*cont*)

Case	RISA			MIT			DIT			Diarrhoea	
	Before	Half way	End	Before	Half way	End	Before	Half way	End	Halfway	End
40	96 5	89 5	97 9				*84 1*	*72 3*	*93 9*	+ + —	+ — —
41	94 4	87 5	91 9				94 7	76 8	78 8	+ + —	+ + +
42	96 3	86 7	91 7				85 9	97 4	57 5	+ + +	+ — —
43	88 0	95 4	94 1	94 8	74 2	87 4				— — —	— — —
44	91 3	91 3	93 4	95 3	85 3	93 5				+ + +	+ — —
45	92 3	*94 2*	93 7	95 4	*80 9*	*97 6*				— — —	— — —
46*	97 6	90 0	94 3	92 7	91 0	90 3				+ + —	+ + —
47	91 7	93 9	91 7							+ — —	+ + —
48	93 0	95 1	93 4							— — —	— — —
49*	97 2	80 3	88 6							+ — —	+ + —
50*	88 9	97 8	97 5							+ + +	+ + —

RISA absorption was investigated in 50 patients (Table 2) The evaluation however excludes a group of 8 subjects who at the beginning of treatment presented an absorption value under 94 per cent of the administered dose — a value generally given as the lower normal limit (LAVIK et coll 1952 CHINN et coll 1952 KIEKENS 1963) Table 4 indicates the average values in the tests carried out in the remaining 42 patients

MIT absorption The absorption values at the beginning of treatment of the present material were slightly lower than those of RISA (Table 1) It would appear that no normal MIT intestinal absorption values are given in the literature for the method followed Twenty of the 24 patients in whom the MIT absorption was evaluated belonged to the group with normal RISA absorption values in the first test and 4 gave values below normal All those investigated were included in the statistical evaluation The average values obtained are presented in Table 5

DIT absorption This presented values more variable and, on the whole lower than those for RISA and MIT in the present material before treatment Again no normal absorption values appear in the literature for this aminoacid

Nine subjects all included in the group having RISA initial absorption values within normal limits were investigated (Table 6)

RISA — MIT association RISA and MIT absorption was investigated at the same time in 24 patients the average values obtained with these two substances in this group are given in Table 7

RISA — DIT association The absorption of RISA and DIT was investigated at the same time in 9 patients Table 8 details the average results obtained for the two substances in this group

Table 3

The types (A, B and C respectively) of reaction (schematic) and the number of patients for the three substances with each reaction

Before	Halfway	End	RISA	MIT	DIT
			17	8	6
			21	11	3
			4	5	0

Discussion

The most important part of the ingested protein is absorbed in the form of aminoacids although it is known that under normal conditions a small quantity of intact proteins and polypeptides is absorbed. Depending on the steric configuration of the molecule, the absorption of aminoacids may occur by active transport or by simple diffusion and take place in elective areas along the small intestine. Tyrosine and its halogenated derivatives are among aminoacids whose absorption mechanisms has been determined. These have been used in this investigation.

NATHANS et coll. (1960) and HUANG (1961) have demonstrated with hamster intestinal loops that only L-tyrosine and its monohalogenated derivatives are absorbed against concentration gradients, while the derivatives di-substituted in 3 and 5 with Br and I, go through the intestinal wall only by means of passive diffusion.

The introduction of the two atoms of halogen induces ionization in the phenolic group and prevents active transport by abolishing the affinity for the carrier.

Among the proteins labelled with radioactive tracers, employed in investigation of intestinal absorption, the most favoured is ^{131}I serum albumin (RISA) which was introduced by LAVIK et coll. (1952) and by CHINN et coll. (1952). The principal advantage of ^{131}I albumin consists in favourable counting conditions when compared with the other proteins used in investigations of this kind, labelled by means of beta emitting isotopes as ^{3}H and ^{14}C and stable isotopes as ^{15}N (JEEJEEBHOY et coll. 1964; CRANE & NEUBERGER 1960). A further

Table 4

RISA absorption Average percentage variations to initial value (Y_0) of values (Y_t) observed halfway and at the end of treatment in fourth column

Treatment	No of patients	Absorption (mean ±SE)	$\left(\frac{Y_t - Y_0}{Y_0}\right)$ ±SE	Significance (t test)
Before	42	96 55±0 259		<0 001
Halfway	4?	90 65±0 974	—6 24±0 93	< 0 01
End	42	91 88±0 973	—4 86±0 95	< 0 01
				> 0 001

Table 5

MIT absorption Average percentage variations to initial value (Y_0) of values (Y_t) observed halfway and at the end of treatment in fourth column

Treatment	No of patients	Absorption (mean ±SE)	$\left(\frac{Y_t - Y_0}{Y_0}\right)$ ±SE	Significance (t test)
Before	24	94 59±0 742		
Halfway	24	88 91±1 368	—5 99±1 38	< 0 01
End	4	91 88±1 079	—2 80±1 24	< 0 0?

Table 6

DIT absorption Average percentage variations to initial value (Y_0) of values (Y_t) observed halfway and at the end of treatment in fourth column

Treatment	No of patients	Absorption (mean ±SE)	$\left(\frac{Y_t - Y_0}{Y_0}\right)$ ±SE	Significance (t test)
Before	9	91 98±1 279		
Halfway	9	79 29±2 162	—13 08±2 68	<0 01
End	9	72 29±4 732	—20 57±5 86	<0 01

advantage of RISA is the slight significance of the recycling phenomena of the tracer the ^{131}I which is released by hydrolysis from the labelled molecules absorbed is in fact almost totally eliminated with the urine owing to the thyroid block induced by the Lugol solution administered on days preceding the test The quantity of isotope which can be re excreted into the intestine is therefore such that it does not affect the measurement of the tracer that has not actually been absorbed

Table 7

RISA and MIT association

Treatment	Substance	Absorption (mean % ± SE)	$\left(\frac{A_t - A_1}{A_1}\right)$ % ± SE
Before	RISA	96.04 ± 0.611	
	MIT	94.59 ± 0.742	
Halfway	RISA	91.93 ± 0.986	−4.17 ± 1.20
	MIT	88.91 ± 1.468	−5.99 ± 1.38
End	RISA	94.60 ± 0.517	−1.42 ± 0.75
	MIT	91.88 ± 1.079	−2.80 ± 1.24

Table 8

RISA and DIT association

Treatment	Substance	Absorption (mean % ± SE)	$\left(\frac{A_t - A_1}{A_1}\right)$ % ± SE
Before	RISA	96.05 ± 0.325	
	DIT	91.98 ± 1.279	
Halfway	RISA	87.91 ± 1.467	− 8.47 ± 1.50
	DIT	79.29 ± 2.162	−13.08 ± 2.68
End	RISA	87.35 ± 2.400	− 9.07 ± 2.41
	DIT	72.29 ± 4.732	−20.57 ± 5.86

On the other hand the aminoacids in the proteins labelled with isotopes of atoms normally present in them such as ^3H and ^{14}C, once they have been absorbed are re-utilized for the synthesis of new molecules which are partly re-excreted into the intestinal lumen. Some authors (JUNQUEIRA et coll. 1955, HANSSON 1959) have in fact demonstrated the presence of labelled pancreatic enzymes as early as 50 to 60 minutes after the intravenous administration of aminoacids labelled with ^{14}C.

The main argument against the use of substances labelled with ^{131}I is the likelihood of release of radioactive iodine before absorption. Several authors have reported deiodinization values varying between 2 and 15 per cent of total radioactivity (LAVIK et coll. 1952, KIEKENS 1963, SHINGLETON et coll. 1955, FREEARK et coll. 1957).

The main conditions causing impairment in protein absorption are the following: (1) insufficiency of the enzymes that perform the hydrolysis of proteins and polypeptides, (2) decrease in the time of contact between the intestinal

content and the surface of the mucosa and (3) destruction or atrophy of the intestinal mucosa

Numerous authors who have investigated the pathologic states in which such conditions occur (KIEKENS 1963 LAVIK et coll 1952 CHINN et coll 1959 HOSAIN & BASU 1960 ALTHAUSEN & UYEYAMA 1954) have pointed out that even in the most serious situations the impairment of protein absorption is generally less significant than that for the other substances investigated at the same time

Only experimental investigations have been carried out on radiation damage of protein intestinal absorption BENNETT et coll (1951) and KISELEV & OKUNOV 1962) demonstrated in irradiated animals after the administration of labelled proteins haematic radioactivity curves less steep than in control animals and ascribed this to a delay in the emptying of the stomach They also tried to evaluate the possibility of diffusion of intact proteins or of high molecular weight polypeptides through the intestinal wall altered by radiation however no positive results were obtained

Evaluation of the present results indicates that in most of the patients investigated therapeutic irradiation of the pelvis impaired the intestinal absorption of proteins The damage was already evident halfway through the treatment (2 500 to 3 000 R) as was observed with other substances previously investigated Generally those patients who halfway through treatment presented no evident impairment had none at the end

Ninety per cent of the patients investigated had altered absorption halfway through the treatment at the end some presented further impairment others an improvement (reactions A and B of Table 3) It should be noted that halfway through the treatment the impairment was significantly different in these two groups of patients the damage in fact was more serious in those patients with improvement at the end of treatment and less marked in those with further impairment

No definite relationship was evident between the frequency of stools and the degree of malabsorption In fact some patients had regular motions or even constipation with altered absorption less frequently absorption was normal in patients with diarrhoea

MIT and RISA produced an equivalent degree of impairment while DIT had a different effect In the group of patients given both MIT and RISA analysis disclosed that the two substances sometimes produced different reactions The most frequent observation for which no satisfactory explanation is at present forthcoming was of more severe impairment arising from MIT particularly at the end of treatment The impairment occasioned by DIT was more marked than by the other substances The severity of the damage produced in all the

Table 7

RISA and MIT association

Treatment	Substance	Absorption (mean % ± SE)	$\left(\frac{X_t - X_1}{X_1}\right)$ % ± SE
Before	RISA	96 04 ± 0 611	
	MIT	94 59 ± 0 742	
Halfway	RISA	91 93 ± 0 986	—4 17 ± 1 20
	MIT	88 91 ± 1 468	—5 99 ± 1 38
End	RISA	94 60 ± 0 517	—1 42 ± 0 75
	MIT	91 88 ± 1 079	—2 80 ± 1 24

Table 8

RISA and DIT association

Treatment	Substance	Absorption (mean % ± SE)	$\left(\frac{X_t - X_1}{X_1}\right)$ % ± SE
Before	RISA	96 05 ± 0 325	
	DIT	91 98 ± 1 279	
Halfway	RISA	87 91 ± 1 467	— 8 47 ± 1 50
	DIT	79 29 ± 2 162	—13 08 ± 2 68
End	RISA	87 35 ± 2 400	— 9 07 ± 2 41
	DIT	72 29 ± 4 732	—20 57 ± 5 86

On the other hand the aminoacids in the proteins labelled with isotopes of atoms normally present in them, such as ^{3}H and ^{14}C, once they have been absorbed are re utilized for the synthesis of new molecules which are partly re excreted into the intestinal lumen Some authors (JUNQUEIRA et coll 1955 HANSSON 1959) have in fact demonstrated the presence of labelled pancreatic enzymes as early as 50 to 60 minutes after the intravenous administration of aminoacids labelled with ^{14}C

The main argument against the use of substances labelled with ^{131}I is the likelihood of release of radioactive iodine before absorption Several authors have reported deiodinization values varying between 2 and 15 per cent of total radioactivity (LAVIK et coll 1952, KIEKENS 1963 SHINGLETON et coll 1955, FREFARK et coll 1957)

The main conditions causing impairment in protein absorption are the following (1) insufficiency of the enzymes that perform the hydrolysis of proteins and polypeptides, (2) decrease in the time of contact between the intestinal

RÉSUMÉ

Les auteurs ont étudie les modifications de l absorption intestinale de RISA MIT et DIT chez des sujets soumis a une telecobalt therapie par des champs abdominaux Ces substances marquees avec ^{131}I et ^{125}I ont éte administrees par voie orale avant au milieu et à la fin du traitement et l activité fecale a eté mesuree L absorption intestinale de ces trois substances est diminuee cependant a un moindre degre que pour les substances étudiées precédemment

REFERENCES

ALTHAUSEN T L and UYEYAMA K A new test of pancreatic function based upon starch tolerance Ann int Med 41 (1954) 563

BENNETT L R CHASTAIN S M DECKER A B and MEAD J F Effect of roentgen irradiation upon protein absorption in the mouse Proc Soc exp Biol (N Y) 77 (1951) 715

CHINN A B LAVIK P S STITT R M and BUCKALOO G W Use of I 131 labeled protein in the diagnosis of pancreatic insufficiency New Engl J Med 247 (1952) 877

CRANE C W and NEUBERGER A The digestion and absorption of protein by normal man Biochem J 74 (1960) 313

DALLA PALMA L Intestinal malabsorption in patients undergoing abdominal radiation therapy *In* Gastrointestinal radiation injury p 261 Edited by M F Sullivan Excerpta Medica Foundation Amsterdam 1968

— BECCIOLINI A CAPPELLINI M et coll Primi rilievi sul comportamento degli acidi biliari totali e di alcuni enzimi pancreatici in pazienti irradiati sulla regione addomino-pelvica (In Italian) Minerva radiol 10 (1965) 279

DE DOMINICIS R e GRECHI G Alterazioni istologiche e istochimiche della mucosa del tenue nei segmenti non colpiti direttamente dal fascio di radiazioni in pazienti irradiati in sede addominale (In Italian) Sperimentale 115 (1965) 82

— — Modificazioni ultrastrutturali della mucosa del tenue umano irradiato (In Italian) Med nucl radiobiol Lat 9 (1966) 435

DE GIULI G DALLA PALMA L and DE DOMINICIS R Prophylaxis and treatment of intestinal damage due to radiation Proc XIth Intern Congress of Radiology Rome September 1965 Int Congress Series No 105 Excerpta Medica Foundation Amsterdam 1967

FREEARK R J KOROLI D D and MEYER K A The use of I 131 labeled albumin in the diagnosis of pancreatic disease Surgery 41 (1957) 268

GIANNARDI G F DE MARZI S RENZI R e CIAMPI G P L assorbimento intestinale del glucosio nei soggetti irradiati sull addome (In Italian) Nuntius radiol 31 (1965) 803

HANSSON E The formation of pancreatic juice proteins studied with labeled amino acids Acta phys scand 46 (1959) Suppl 161

HOSAIN F and BASU S R Pancreatic insufficiency test with low doses of radio iodised human serum albumin Medica mundi 6 (1960) 68

HUANG K C Intestinal absorption of L Tyrosine derivates Feder Proc 20 (1961) 246

JEEJEEBHOY K N STEWART J H EVANS E A and BOOTH C C On the use of tritium labeled albumin for studies of intestinal absorption Gut 5 (1964) 346

JUNQUEIRA L C U HIRSCH G C and ROTSCHILD H A Glycine uptake by the rat pancreatic juice Biochem J 61 (1955) 275

9 patients investigated was much greater with DIT either halfway through or at the end of treatment As regards the effect *in individual patients it should* be noted that in none of them was no impairment of DIT absorption evident in both tests, while only in 3 patients did the absorption return to normal at the end of treatment

These data seem to suggest that the prevailing damage caused by irradiation in the intestinal absorption affects the mechanism of parietal transit while the hydrolytic processes occur to a normal degree This is probably dependent on the high concentration of proteolytic enzymes in the intestine during the passage of food and which is markedly in excess of physiologic needs

Furthermore, investigations carried out by DALLA PALMA et coll (1965) on the alteration of pancreatic and biliary secretions, demonstrated that the activity of the pancreatic enzymes never decreased so grossly as to suggest a possible impairment of the digestion of proteins taken with food

As regards RISA and MIT the damage proved less significant than that occurring with other substances previously investigated, as can be seen by comparison of the present data with those in Table 1 relating to the previous research

The present work has contributed further information concerning the state of malabsorption induced by abdominal irradiation and confirms the results already reported

Acknowledgements

The authors are indebted to Dr R Renzi for his helpful suggestions This work was supported by a grant from Consiglio Nazionale delle Ricerche

SUMMARY

Changes in the intestinal absorption of RISA MIT and DIT in patients undergoing telecobalt therapy through abdominal fields were investigated These substances labelled with ^{131}I and ^{1} I were administered by mouth before *halfway through and at the end of treat*ment and the faecal activity was measured An impairment of intestinal absorption of all three compounds occurred although to a lesser degree than in those previously investigated

ZUSAMMENFASSUNG

Es wurden die Änderungen der Absorption des Darmes fur RISA MIT und DIT bei Patienten die bei der Telecobalt Therapie mit abdominalen Feldern bestrahlt wurden untersucht Diese mit ^{131}I und ^{1} I gezeichneten Substanzen wurden per os vor halbwegs und am Ende der Therapie verabfolgt und die Aktivitat der Fakalien gemessen Eine Storung der intestinalen *Absorption fur alle drei* Substanzen war wenn auch in geringerem Umfang als bei fruher untersuchten Substanzen nachweisbar

RÉSUMÉ

Les auteurs ont etudie les modifications de l absorption intestinale de RISA MIT et DIT chez des sujets soumis a une telécobalt therapie par des champs abdominaux Ces substances marquees avec ^{131}I et ^{125}I ont ete administrees par voie orale avant au milieu et a la fin du traitement et l activite fécale a été mesuree L absorption intestinale de ces trois substances est diminuee cependant a un moindre degre que pour les sub tances etudiees précedemment

REFERENCES

ALTHAUSEN T L and UYEYAMA K A new test of pancreatic function based upon starch tolerance Ann int Med 41 (1954) 563

BENNETT L R CHASTAIN S M DECKER A B and MEAD J F Effect of roentgen irradiation upon protein absorption in the mouse Proc Soc exp Biol (N Y) 77 (1951) 715

CHINN A B LAVIK P S STITT R M and BUCKALOO G W Use of I 131 labeled protein in the diagnosis of pancreatic insufficiency New Engl J Med 247 (1952) 877

CRANE C W and NEUBERGER A The digestion and absorption of protein by normal man Biochem J 74 (1960) 313

DALLA PALMA L Intestinal malabsorption in patients undergoing abdominal radiation therapy *In* Gastrointestinal radiation injury p 261 Edited by M F Sullivan Excerpta Medica Foundation Amsterdam 1968

— BECCIOLINI A CAPPELLINI M et coll Primi rilievi sul comportamento degli acidi biliari totali e di alcuni enzimi pancreatici in pazienti irradiati sulla regione addomino-pelvica (In Italian) Minerva radiol 10 (1965) 279

DE DOMINICIS R e GRECHI G Alterazioni istologiche e istochimiche della mucosa del tenue nei segmenti non colpiti direttamente dal fascio di radiazioni in pazienti irradiati in sede addominale (In Italian) Sperimentale 115 (1965) 82

— — Modificazioni ultrastrutturali della mucosa del tenue umano irradiato (In Italian) Med nucl radiobiol Lat 9 (1966) 435

DE GIULI G DALLA PALMA L and DE DOMINICIS R Prophylaxis and treatment of intestinal damage due to radiation Proc XIth Intern Congress of Radiology Rome September 1965 Int Con ress Series No 105 Excerpta Medica Foundation Amsterdam 1967

FREEARK R J KOROLS D D and MEYER K A The use of I 131 labeled albumin in the diagnosis of pancreatic disease Surgery 41 (1957) 268

GIANNARDI G F DE MARZI S RENZI R e CIAMPI G P L assorbimento intestinale del glucosio nei sogg tti irradiati sull addome (In Italian) Nuntius radiol 31 (1965) 803

HANSSON E The formation of pancreatic juice proteins studied with labeled amino acids Acta phys scand 46 (1959) Suppl 161

HOSAIN F and BASU S R Pancreatic insufficiency test with low doses of radio iodised human serum albumin Medica mundi 6 (1960) 68

HUANG K C Intestinal absorption of L Tyrosine derivates Feder Proc 20 (1961) 246

JEEJEEBHOY K N STEWART J H EVANS E A and BOOTH C C On the use of tritium labeled albumin for studies of intestinal absorption Gut 5 (1964) 346

JUNQUEIRA L C U HIRSCH G C and ROTSCHILD H A Glycine uptake by the rat pancreatic juice Biochem J 61 (1955) 275

KIEKENS R Digestion and digestive absorption of fats and protein in the normal subject and after gastrectomy Acta gastro ent belg 26 (1963) 401
KISELEY P N and OKULOV N M Disturbance in the process of absorption of various substances from the gastrointestinal tract during radiation injury *In* Problem of radiology Vol 2 p 166 Edited by M V Pobedinskii 1962
LAVIK P S MATTHEWS R W BUCKALOO G W et coll Use of I 131 labeled protein in the study of protein digestion and absorption in children with and without cystic fibrosis of pancreas Pediatrics 10 (1952) 667
NATHANS D TAPLEY D I and ROSS J E Intestinal transport of amino acids studied in vitro with labeled I[131] MIT Biochim Biophys Acta 41 (1960) 277
POLACHEK A A, COPE C B WILLIARD R F and BARNES F W I 131 labeled protein and fat meals in patients with chronic pancreatitis Gastroenterology 37 (1959) 38
RATZKOWSKI E and HOCHMAN A Gastro intestinal function after abdominal cobalt irradiation Acta radiol Ther Phys Biol 7 (1968) 417
SHINGLETON W W WELLES M H BAYLIN G J et coll The use of radioactive labeled protein and fat in the evaluation of pancreatic disorders Surgery 38 (1955) 2

FROM DONNER LABORATORY AND DONNER PAVILION, LAWRENCE RADIATION LABORATORY UNIVERSITY OF CALIFORNIA BERKELEY CALIFORNIA U S A

RELATIVE BIOLOGIC EFFECTIVENESS AND OXYGEN ENHANCEMENT RATIO AT VARIOUS DEPTHS OF A 910 MeV HELIUM ION BEAM

by

M R Raju M Gnanapurani U Madhvanath J Howard and J T Lyman

The 910 MeV helium ion beam from the 184 inch synchrocyclotron at Berkeley has long been used mainly for pituitary irradiations When the narrow Bragg peak is broadened by using a variable absorber in the beam it is possible to use this beam for other radiotherapeutic applications In such cases the dose contribution from the high LET components at the broadened Bragg peak region is small However the experimental determination of the oxygen enhancement ratio (OER) of 1 6 for 14 MeV neutrons indicates that a small fraction of dose due to alpha particles produced by 14 MeV neutrons in tissue is mainly responsible for reducing the OER (Neary & Savage 1964 Barendsen & Broerse 1966) It is of interest to find out how a small fraction of dose due to high LET components at the broadened Bragg peak region would affect the radiobiologic properties of therapeutic interest such as relative biologic effectiveness (RBE) and oxygen enhancement ratio Such measurements will be helpful

Submitted for publication 23 July 1970

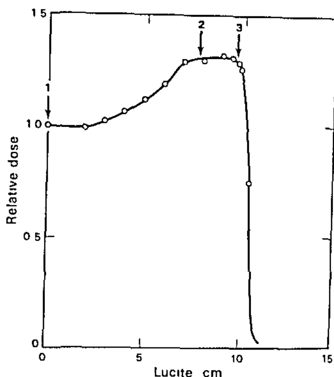


Fig. 1. Modified depth dose distribution of a 910 MeV helium ion beam used with a ridge filter showing the three exposure positions.

in assessing the therapeutic capabilities of this radiation. With this in view, preliminary experiments were performed with cultured human kidney cells.

Materials and Methods. The tissue culture techniques for human kidney cells (T 1) used by BARENDSEN et coll. (1960) and TODD (1964) were used in this investigation. Feeder cells exposed to 4 000 to 5 000 rad of roentgen rays were plated in 35 mm Petri dishes (5×10^4 per dish) and they were incubated overnight. Cells in early logarithmic growth phase were plated in these dishes in appropriate numbers so that surviving colonies would be about 100 on each dish. The dishes were placed in the incubator at 37° C for 4 to 7 hours, before exposure to radiation.

The sample loading wheel as described by TODD et coll. (1968) was used. The medium was removed from the dishes before they were mounted in the wheel. Air or nitrogen saturated with water vapor was admitted into the wheel and circulated over the dishes during exposure. In the case of nitrogen, the cells were nitrogenated for at least 5 minutes before exposure to radiation.

The Bragg peaks of monoenergetic charged particle beams are narrow when compared with typical tumor sizes. The technique for modifying the depth dose distribution of monoenergetic charged particles to uniformly irradiate the treatment volume is usually to use ridge filters (KARLSSON 1964, RAJU et coll. 1969).

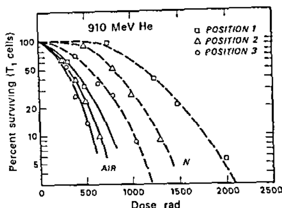


Fig 2 Survival curves for T 1 cells exposed under aerobic and anoxic conditions at the three positions

A 910 MeV helium ion beam has a range of about 32 cm in water This energy is much higher than is necessary for radiotherapeutic applications Such high energy heavy charged particle beams give a lower ratio of do es at the peak to the entrance because of multiple cattering effects and the loss of the particles before they reach the peak The beam i first degraded by using 3 2 cm of copper The residual energy of the beam after passing through copper is a little over 500 MeV This re idual beam is further modified by using a ridge filter so that the peak of the depth dose distribution is broad enough to cover about 4 cm of lucite Such a distribution is shown in Fig 1 Dishes containing cells were expo ed to different do es of radiation at three po itions marked 1 2 and 3 in Fig 1 Three dishe containing cells were expo ed for each do e point Twelve to 15 days after exposure the colonies were fixed in Bouin s fluid and stained with Harris hemotoxylin All the visible colonies were counted and the percentage survival calculated

Results

Figure 2 gives the survival curves obtained for the three positions on the depth do e distribution mentioned above Biologic effectiveness compared with that of the plateau position (marked 1 in Fig 1) and OER were calculated in the surviving fraction region of 10 %

The biologic effect at the plateau is very similar to that of conventional radiation The biologic effectiveness at positions 2 and 3 compared with position 1 is 1 1 and 1 3 respectively The OER values at positions 1 2 and 3 are 2 5 2 and 1 8 respectively These preliminary results indicate that there is a significant reduction in OER in the broad peak region If the exposures were made with two opposing fields one could obtain an average OER of 2 over a 4 cm wide region

The trend of this variation of RBE and OER over the peak region can be expected from variation of LET, which increases with depth. Early experiments with mammalian tumor cells that are anoxic, studied in vivo, indicate that the dose *response* was significantly altered at the broadened Bragg peak of a 910 MeV helium ion beam when compared with that at the entrance (BERRY & ANDREWS 1964).

A high energy helium ion beam may have a radiotherapeutic application in the treatment of deep seated tumors located near sensitive and vital *structures* because of its depth dose characteristics. In addition, the significant reduction in OER indicates an additional advantage of high energy helium ion beams in treating tumors containing anoxic cells.

Acknowledgements

This work was supported by the U. S. Atomic Energy Commission. M. R. Raju is grateful to Dr. G. W. Barendsen for introducing him to tissue culture work. We wish to thank Mrs. Catharine D. Boerke for her suggestions in maintaining a tissue culture laboratory.

SUMMARY

The relative biologic effectiveness (RBE) and oxygen enhancement ratio (OER) at different points on the ridge filter modified depth dose distribution of a 910 MeV helium ion beam is measured by using human kidney cells (T 1). The results indicate that the RBE at the broad peak region is about 1.2 compared to that at the beam entrance (plateau) and the OER is found to be about 2.0. This significant reduction in OER may be helpful in *treatment of deep seated tumors containing anoxic cells*.

ZUSAMMENFASSUNG

Die relative biologische Wirksamkeit (RBW) und das Verhältnis des durch Sauerstoff gesteigerten Strahleneffektes (OER) an verschiedenen Punkten einer durch einen gewölbten Filter veränderten Tiefen-Dosis-Verteilung eines 910 MeV Helium-Ionenstrahl wurden unter Anwendung menschlicher Nierenzellen (T 1) gemessen. Aus den Ergebnissen geht hervor, dass die RBW verglichen mit derjenigen des Eingangsplateaus des Strahlenganges im Bereich des breiten Gipfels etwa 1.2 und die OER etwa 2.0 beträgt. Die signifikante Erniedrigung der OER mag bei der Behandlung tiefliegender Tumoren, die anoxische Zellen enthalten, nützlich sein.

RÉSUMÉ

Les auteurs ont mesuré l'efficacité biologique relative (RBE) et l'effet oxygène (OER) en différents points de la distribution de dose en profondeur d'un faisceau ionique d'hélium de 910 MeV modifiée par un filtre de crête au moyen *de cellules de rein humain* (T 1). Les résultats montrent que l'efficacité biologique relative dans la région du pic large est de 1.2 par rapport à celle de l'entrée du faisceau (plateau) et que l'effet oxygène est d'environ 2.0. Cette importante réduction de l'effet oxygène peut être utile pour le traitement de tumeurs situées en profondeur contenant des cellules anoxiques.

REFERENCES

BARENDSEN G W and BROERSE J J Dependence of the oxygen effect on the energy of fast neutrons Nature 212 (1966) 722

— BEUSKER T L J VERGROESEN A J and BUDKE L Effects of different ionizing radiations on human cells in tissue culture II Biological experiments Radiat Res 13 (1960) 841

BERRY R J and ANDREWS J R The response of mammalian tumor cells in vivo to radiations of differing ionizing densities (LET) Ann N Y Acad Sci 114 (1964) 48

KARLSSON B G Methoden zur Berechnung und Erziehung einiger fur die Tiefentherapie mit hochenergetischen Protonen gunstiger Dosisverteilungen Strahlentherapie 124 (1964) 481

NEARY G J and SAVAGE J R K Oxygen effect with 14 MeV neutrons Nature 204 (1964) 197

RAJU M R LYMAN J T BRUSTAD T and TOBIAS C A Heavy charged particle beams *In* Radiation dosimetry Vol III p 151 Edited by F H Attix and E Tochilin Academic Press New York and London 1969

TODD P W Reversible and irreversible effects of ionizing radiations on the reproductive integrity of mammalian cells cultured in vitro Ph D thesis Lawrence Radiation Laboratory Report UCRL 11614 (1964)

— LYMAN J T ARMER R A et coll Dosimetry and apparatus for heavy ion irradiation of mammalian cells in vitro Radiat Res 34 (1968) 1

FROM THE DEPARTMENT OF GYNECOLOGY (DIRECTOR: PROF. H. L. KOTTMEIER), AND THE SECTION OF DIAGNOSTIC RADIOLOGY (DIRECTOR: G. LAGERGREN), RADIUMHEMMET, STOCKHOLM, SWEDEN

TRANSVERSE AXIAL TOMOGRAPHY AS AN ADJUNCT IN RADIOTHERAPY OF CARCINOMA OF THE UTERINE CERVIX

by

INGEMAR JOELSSON

An appraisal of the dynamic topographic relationship of the pelvic visceral organs has been the concern of the radiotherapist in the treatment of carcinoma of the uterine cervix. Attempts have been made to assess the variability of position as well as to delineate in each patient the distance between the tumor requiring a cancerocidal dose of radiation and the healthy tissue that should not be compromised. Investigations have not yielded useful results, mainly because of the difficulty in appraising the solid geometry of the pelvic content from roentgenograms taken in perpendicular planes or produced by the focus shift method. The pattern in the films formed by the anatomic structures of interest is frequently obscured by adjacent organs. It was therefore thought that the anatomic relation between the uterine cervix, the urinary bladder and the rectum might be individually determined by means of transverse tomography by the method described by TAKAHASHI (1965, 1969).

This work was supported by grants from the Cancer Society of Stockholm and the King Gustaf V Jubilee Fund. Submitted for publication 30 June 1970.

Material and Methods Ten patients with carcinoma of the uterine cervix, stage I—IIb were studied The patients were first examined with a p and cross-table lateral roentgenograms and radiopaque centimeter scales were positioned parallel to the longitudinal axis of the body As the next procedure the patients were examined by transverse axial tomography (To hiba Model CS BC) with a metal ring sutured about the portio of the cervix a metal cylinder 6 mm in diameter was at the same time in erted into the cervical canal All patients received 20 ml Urografin instilled into the emptied bladder through a catheter after 20 ml barium emulsion had been introduced into the rectum If the examination lasted more than 30 minutes the bladder was re emptied and another injection of Urografin made Consecutive body sections 1 cm apart, were exposed starting 3 cm caudal to the cranial border of the symphysis pubis The last section was exposed 7 cm cephalad to the cranial border of the symphysis pubis

The tomograms were taken with a constant magnification factor (M) of 1 33 and the series of photographs were redrawn to true size by means of an optical system The distance between the center of the cervical cylinder and the clo est part of the urinary bladder or rectum was measured in hose ections where the outlines were discernible

It is appreciated that in the tomographic method the thickness of the layer (t) depicted is a function of the maximally tolerated blur (B_m) according to the equation

$$t=B_m \times \cot\theta \times \frac{1}{M}$$

where θ is the angle between the central roentgen ray and the normal to the tomographic plane in this case 70 (MEREDITH & MASSEY 1968) The acceptance of 1 5 mm of blur means the representation in one film of a 0 4 mm thick tissue layer in practice, however the layer is somewhat thicker due to the effect of the screens and to other factors although the limits are still adequate for the validity of the measurements in this investigation

Results

Rectum The distance between the center of the cylinder in the cervical canal and the clo est contour of the rectum varied considerably in the tomographic section in this series of patients (Table 1) In one of the patients (aged 49 stage Ib carcinoma) the distance was only 9 mm and in another (aged 51 stage IIa carcinoma) the distance was 34 mm The transverse sections that were suitable for measurements of the cervical rectal distance lay in a region between 1 and 6 cm cephalad to the upper border of the symphysis pubis The maximal dif

Table 1

Distance in mm between the center of the cervical canal and the closest part of the contrast coated rectal mucosa measured in transverse body sections from 1 to 6 cm cephalad to the cranial border of the symphysis pubis

Patient No	Cephalad to the cranial border of the symphysis pubis					
	1 cm	2 cm	3 cm	4 cm	5 cm	6 cm
1		16	19	16		
2			16	14		
3		11	12			
4				34		14
5		24	34	32		
6	18	15				
7					26	21
8				16	9	
9		21	22	12		
10			21	17		

ference in measured distance between the center of the cervical canal and the bowel wall, comparing one section with the next consecutive one, was 10 mm

The cervical rectal distance as well as the cervical rectal topography varied The rectum was usually located on the right side of the genital canal in the transverse sections caudal to the portio (Figs 1 and 2) The distance between the center of the cervix and the rectum was at a minimum in the sections taken *through that part of the uterine cervix between the portio and the vault of the* posterior fornix The rectum in this region was consistently located directly posterior to the cervix and in 5 of the 10 patients the bowel here changed from a right sided to a left sided position relative to the genital canal (Figs 3 and 4) The bowel adopted a left sided position in relation to the cervical canal from the level of the cranial part of the posterior vaginal fornix and in a cephalad direction (Fig 5)

Bladder The distance between the center of the cervical canal and the closest part of the urinary bladder was measurable in the transverse sections taken over a 7 cm long region in the cephalad direction starting at the cranial border of the symphysis pubis (Table 2) The range of distances between the structures was 14 to 32 mm *The maximal variation between the consecutive sections in one* patient was 16 mm In 3 out of 10 patients the lateral border of the bladder projected in a dorsal direction more than a centimeter posterior to the cervical canal An example of this appears in Fig 1

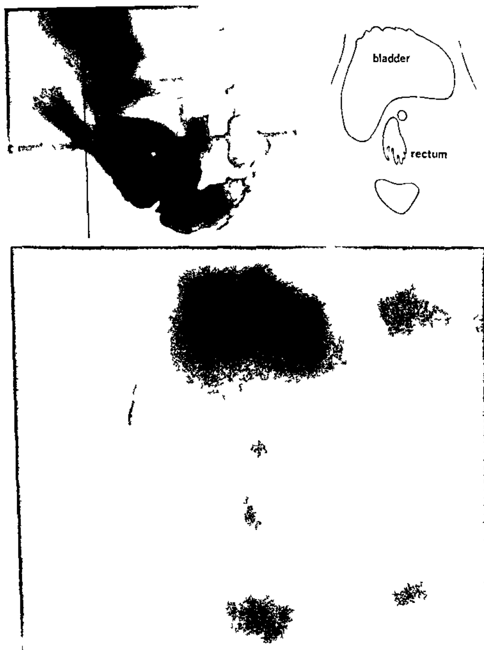


Fig 1 T ans erse body section through the upper part of the vagina caudal to the portio The po t on of the plane i nd cated in th lateral roentgenogram

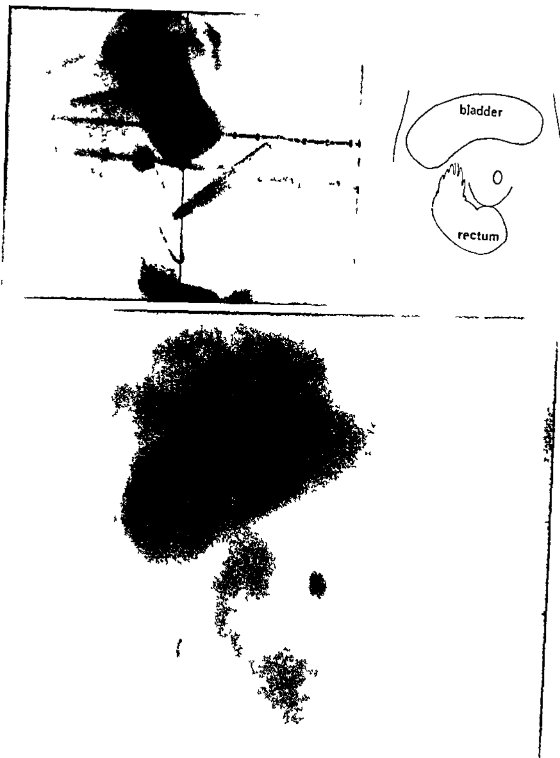


Fig 2 Transver e body ecti n through the upper part of the vagina at the level of the portio

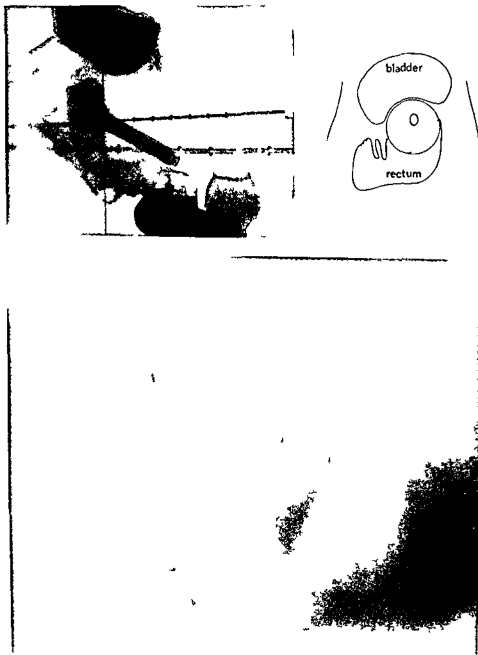


Fig 3 Tr n rs tomogram through the d stal part of the uterine cervix

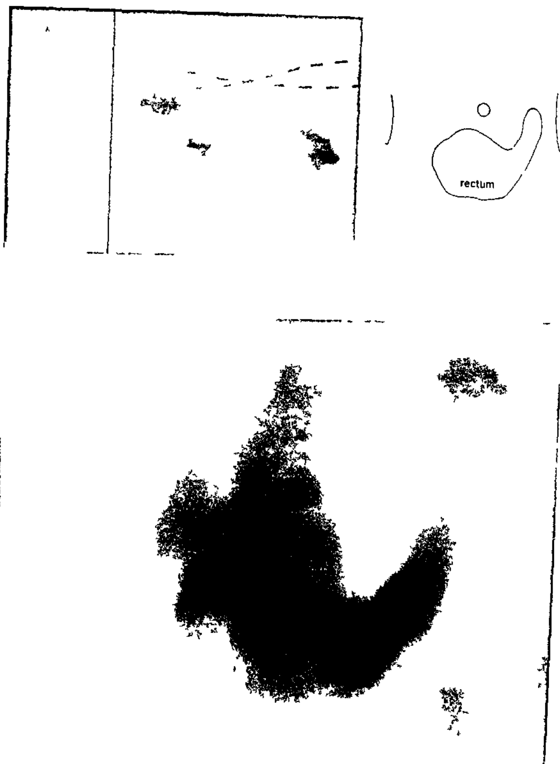


Fig. 4. Tomogram through the uterine cervix caudal to the dome of the posterior vaginal fornix



Fig 5 Tomograph c section through the ı thmus of the uterus

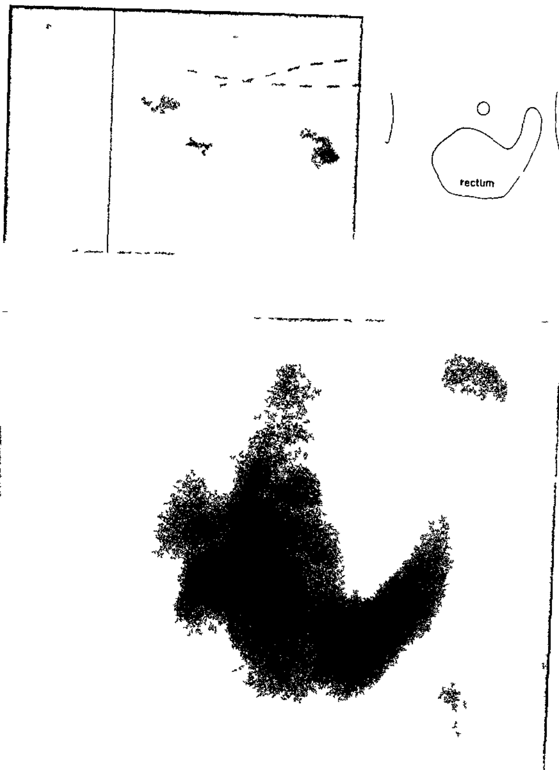


Fig 4 Tomogram through the uterine cervix caudal to the dome of the posterior vaginal fornix

occupies a considerable part of the pelvis directly posterior to the uterine cervix at this level In some of these tomographic sections the breadth of the rectum may be 10 cm or more The same is true regarding the bladder The e anatomic fact play an important role for the understanding of the occurrence of complications produced by the primary radiotherapy It would therefore seem reasonable that the use of routine transverse axial tomography could be of help in treatment planning and coordination of therapy in carcinoma of the uterine cervix The method would especially facilitate the correct placement of the shielding blocks in the external radiation beams

Figures have been given in this presentation regarding the distance between the center of the cervical canal and the viscera as determined from the margin of the contrast coated mucous membranes of the urinary bladder and the rectum It should be remembered however that these figures are only indicative of the close relationship between the structures portrayed

The method of transverse axial tomography carries with it inherent sources of errors On the one hand the tomographic motion blur of details outside the tomographic layer may simulate closer spatial relationships between two structures than exists in reality On the other hand all distances measured on the tomograms lie in transverse planes If the true minimal distances between the structures form an angle with the transverse plane, the measured distances will necessarily be exaggerated Since the axes of the genital canal and the distal colon are seldom parallel to the long axis of the patient the true distance between the cervix and the rectum are usually less than those measured

A difficulty in transverse axial tomography lies in the uncertainty of translation from the tomographic layer in a cranio-caudal direction of the body to the point of its intersection with the anterior body contour The cranial border of the symphysis pubis is often used as an anatomic reference in clinical routine but it is seldom possible to define it with an uncertainty under ± 0 5 cm This is due to the rounded shape of the bone and to the variable but usually thick layer of subcutaneous fat over the symphysis of the female Furthermore the variation in inclination of the pelvis in supine position causes an uncertainty regarding the intersection with a central or posteriorly located pelvic structure of a strictly transverse plane the position of which is determined by its relation to the anterior body surface A p with or without cross table lateral roentgenograms are therefore needed together with the tomogram for the precise indication of the position of the tomographic layer

Conclusion

Transverse axial tomography of the pelvic region revealed that the rectum usually occupied a considerable part of the pelvis directly posterior to the uterine

Table 2

Distance in mm between the center of the cervical canal and the closest part of the contrast-coated bladder mucosa measured in transverse body sections from 0 to 7 cm cephalad to the symphysis pubis

Patient No	Cephalad to the cranial border of the symphysis pubis							
	0 cm	*1 cm*	*2 cm*	*3 cm*	*4 cm*	*5 cm*	*6 cm*	*7 cm*
1				14	23			
2				14	21			
3		21	14	16	18			
4					15			
5			22	24				
6	16	27	11					
7						30	24	20
8					24	20	25	
9			27	25	32			
10				24	21	18		

Discussion

Irrespective of the therapeutic modality, the significance of determining the anatomic relationship between the uterine cervix and the distal portion of the large intestine as well as the posterior wall of the urinary bladder in each patient is obvious to the radiotherapist involved in the coordination between intracavitary and external radiation treatment in gynecology.

Several years ago the patients at Radiumhemmet were examined with stereoscopic roentgenograms during the intracavitary treatment courses. The information that was needed for estimation of the radiation dose at the posterior wall of the bladder or at the anterior wall of the rectum was, however, not provided by this method. Although other procedures were tried, for example three dimensional reconstruction techniques, the computation of bladder and rectal doses from direct measurements of dose rates became the method of choice in clinical routine. Measured dose rates at the posterior wall of the bladder along the urethra and at the anterior wall of the rectum also serve in the detailed planning of the combined intracavitary and external therapy. The decision whether or not a shielding block should be used is for example made from a consideration of the obtained measurement values. The proper interpretation of these data is that the dose values represent doses of clinical significance in the immediate periphery of the uterine cervix, or, viewed another way, at the outer contour of the tumor. It has been observed in the present study that the bowel changes from a right sided to a left sided position in the pelvis in the region of the posterior fornix of the vagina. The tomograms demonstrated that the rectum

occupies a considerable part of the pelvis directly posterior to the uterine cervix at this level In some of these tomographic sections the breadth of the rectum may be 10 cm or more The same is true regarding the bladder These anatomic facts play an important role for the understanding of the occurrence of complications produced by the primary radiotherapy It would therefore seem reasonable that the use of routine transverse axial tomography could be of help in treatment planning and coordination of therapy in carcinoma of the uterine cervix The method would especially facilitate the correct placement of the shielding blocks in the external radiation beams

Figures have been given in this presentation regarding the distance between the center of the cervical canal and the viscera as determined from the margin of the contrast coated mucous membranes of the urinary bladder and the rectum It should be remembered however that these figures are only indicative of the close relationship between the structures portrayed

The method of transverse axial tomography carries with it inherent sources of errors On the one hand, the tomographic motion blur of details outside the tomographic layer may simulate closer spatial relationships between two structures than exists in reality On the other hand all distance measured on the tomograms lie in transverse planes If the true minimal distances between the structures form an angle with the transverse plane the measured distances will necessarily be exaggerated Since the axes of the genital canal and the distal colon are seldom parallel to the long axis of the patient the true distance between the cervix and the rectum are usually less than those measured

A difficulty in transverse axial tomography lies in the uncertainty of translation from the tomographic layer in a cranio caudal direction of the body to the point of its intersection with the anterior body contour The cranial border of the symphysis pubis is often used as an anatomic reference in clinical routine but it is seldom possible to define it with an uncertainty under ± 0 5 cm This is due to the rounded shape of the bone and to the variable but usually thick layer of subcutaneous fat over the symphysis of the female Furthermore the variation in inclination of the pelvis in supine position causes an uncertainty regarding the intersection with a central or posteriorly located pelvic structure of a strictly transverse plane the position of which is determined by its relation to the anterior body surface A p with or without cross-table lateral roentgenograms are therefore needed together with the tomogram for the precise indication of the position of the tomographic layer

Conclusion

Transverse axial tomography of the pelvic region revealed that the rectum usually occupied a considerable part of the pelvis directly posterior to the uterine

cervix, the distance between the rectum and the center of the cervical canal was minimal in the region of the posterior fornix of the vagina The urinary bladder was observed to rest around the anterior aspect of the cervix, with the lateral parts of the bladder extending even posterior to the level of the cervical canal

Acknowledgement

The author wishes to thank Professor Paul Edholm for valuable help and discussions

SUMMARY

Transverse axial tomography has been used in a series of patients with carcinoma of the uterine cervix stage I—IIb The wide variability in the topographic relationship between the uterine cervix the urinary bladder and the rectum was confirmed It is suggested that the method could be a valuable addition to the planning of radiotherapy in carcinoma of the uterine cervix

ZUSAMMENFASSUNG

In einer Serie von Patienten mit einem Carcinom des Uterus Halses Stadium I—IIb wurde eine transversale Axial Tomographie ausgeführt Die grosse Variabilität der topographischen Beziehung zwischen Cervix uteri Blase und Rectum wurde bestätigt Es liegt auf der Hand dass diese Methode eine wertvolle Erweiterung bei der Planlegung der Radiotherapie des Carcinoms des Uterus Halses sein kann

RÉSUMÉ

L'auteur a utilisé la tomographie axiale transverse chez une série de malades atteintes de cancer du col de l'utérus aux stade I—IIb La grande variabilité des rapports topographiques entre le col utérin la vessie et le rectum est confirmée L'auteur pense que cette méthode pourrait être un complément intéressant pour établir le plan de radiothérapie d'un le cancer du col utérin

REFERENCES

MEREDITH W J and MASSEY J B Fundamental physics of radiology John Wright & Sons Bristol 1968

TAKAHASHI S Conformation radiotherapy Rotation techniques as applied to radiography and radiotherapy of cancer Acta radiol (1965) Suppl No 242

— An atlas of axial transversal tomography and its clinical application Springer Verlag Berlin 1969

FROM THE RADIATION PHYSICS DEPARTMENT (DIRECTOR PROF G HETTINGER), UNIVERSITY OF UMEA, SWEDEN

DOSIMETRIC MEASUREMENTS AT THE NORDIC MEDICAL ACCELERATORS

I Characteristics of the radiation beam

by

H SVENSSON and G HETTINGER

National Standard laboratories can often provide a certain calibration service for determining absorbed doses of low energy roentgen rays and ^{60}Co γ radiation for radiotherapy Similarly developed routines are not available for electron and photon radiation emitted by betatrons or linear accelerators Several intercomparisons of the absorbed dose at a reference point in the central ray have however been carried out by different laboratories The dosimeters ferrous sulfate or TLD were sent to different laboratories irradiated, and then returned for evaluation (PETTERSSON 1967a EHRLICH & LAMPERTI 1969 HOLT et coll 1969 and LOEVINGER et coll 1969 etc) Even though agreement between absorbed dose determinations is obtained at a reference point large discrepancies can remain in the dosimetry since the measuring techniques for determining depth dose and isodose curves often differ

WEBSTER & TSIEN (1965) have grouped together isodose curves from institutions and accelerator manufacturers in 15 countries for roentgen radiation between 7 and 35 MeV Definite conclusions regarding the variations of isodose curves between different accelerators and laboratories are however impossible

Submitted for publication 13 July 1970

Table 1

Clinics visited during the tour in 1968

Clinic	Chief radiotherapeut and physicist	Accelerator manufacturer	Radiation	Maximum energy
Denmark				
Radiumstationen Copenhagen	H. Johansen J. Ambrosen	BBC	e^- rtg rays	35 MeV
		Varian	rtg rays	6 MeV
		Varian	rtg rays	6 MeV
Radiumstationen Odense	P. B. Hansen P. Omsveen	BBC	e^- rtg rays	35 MeV
Radiumstationen Aarhus	S. Kaae C. B. Madsen	BBC	e^- rtg rays	35 MeV
Finland				
Strålbehandlingskliniken Helsinki	I. R. Holsti E. Spring	BBC	e^- rtg rays	35 MeV
		BBC	e^- rtg rays	35 MeV
Norway				
Det Norske Radium hospital Oslo	F. Poppe T. Brustad	BBC	e^- rtg rays	31 MeV
		BBC	e^- rtg rays	37 MeV
		Siemens	e^- rtg rays	18 MeV
Sweden				
Konung Gustaf V:s Jubileumsklinik Gothenburg	M. Strandqvist H. Skoldborn	BBC	e^- rtg rays	35 MeV
		AEI	rtg rays	5 MeV
Radiologiska kliniken Lund	M. Lindgren K. Liden	BBC	e^- rtg rays	35 MeV
Radiumhemmet Stockholm	J. Einhorn R. Walstam	Siemens	e^- rtg rays	18 MeV
		Varian	rtg rays	6 MeV
Konung Gustaf V:s Jubileumsklinik Umeå	L. G. Larsson C. Hettinger	BBC	e^- rtg rays	35 MeV
Akademiska sjukhuset Uppsala	B. Nohrmann J. Cederlund	BBC	e^- rtg rays	35 MeV
Radioterapeutiska kliniken Örebro	O. Hallberg K. J. Vikterlof	Siemens	e^- rtg rays	42 MeV

since the radiation beams are often defined and measured in different ways and different methods are employed for determining the dose distribution. It is necessary to describe the radiation field in a uniform way in order to render intercomparisons of depth dose and isodose curves from different accelerators and laboratories meaningful. The International Commission on Radiological Units and Measurements (ICRU), Report No. 10 d (1963) recommends methods

appropriate to energies below about 2 MeV for the qualitative specification of photon radiation and for the absorbed dose measurements the Sub committee on Radiation Dosimetry (SCRAD) of the American Association of Physicists in Medicine (1966) proposed similar recommendations for the electron beams up to 50 MeV

The present paper summarizes a series of measurements made with different accelerators in Denmark Finland Norway and Sweden (Table 1) in order to investigate the possibilities of creating uniform and simple beam definitions with high energy roentgen rays and electron radiation The tour took place during 3 months in 1968 and included visits to 11 laboratories with 14 betatrons and 4 linear accelerators Measurements of the absorbed dose in a water phantom using these uniformly defined radiation beams will be summarized in another paper (SVENSSON 1971a) discrepancies in depth dose and isodose curves arising from differences in the constructional details of the accelerators will also be discussed

Experiments

To allow each radiotherapy centre with an accelerator to define the radiation beam in a uniform way simple beam parameters should be recommended and simple and conventional measuring equipment used The beam parameters determined in this investigation have been measured with elementary equipment which was transported in a small car between the 11 laboratories

The energy of roentgen rays and electron beams When electrons leave the acceleration orbit and meet the target roentgen rays are produced whose maximum energy is equal to the kinetic energy of the electrons If the electrons are withdrawn for electron therapy however their energy is reduced by the window of the vacuum tube by scattering foils by possible monitor chambers and by the air between the tube window and the patient In principle two kinds of energy calibration are thus needed one for roentgen rays and one for electron beams

The energy calibration of roentgen rays was carried out with 11 betatrons by studying thresholds for $(\gamma\ n)$ reactions with ^{12}C ^{16}O and ^{63}Cu (18 7 15 7 and 10 8 MeV respectively) in accordance with recommendations given by SCRAD (1966) Water *n* heptane (pro analysi) and granulated copper were used as test samples Water and *n* heptane were irradiated in plastic containers The pure isotope of copper ^{63}Cu has been used in similar measurements by ALMOND (1967) Tests showed however that chemically pure copper containing both ^{63}Cu and ^{65}Cu could be used The copper sample was irradiated in a cadmium container so that as small a background activity as possible should arise from ac

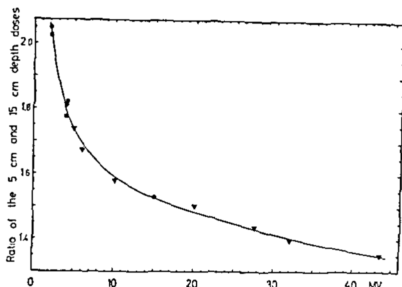


Fig 1 The ratio of the 5 cm and 15 cm depth doses (SSD 100 cm field size 10×10 cm) as a function of the maximum photon energy The relative depth doses and MV are taken from HPA (1961) ● GREENE (1969) ■ and from the present investigation ▼ The values from GREENE have been measured with different accelerators by different laboratories

tivation by thermal neutrons The measurements of the irradiated samples were carried out with a liquid GM tube

Threshold value determinations were similarly carried out with two of the betatrons using the reaction ^{16}O (γ, 2*n*) The threshold value was taken to be 28 9 MeV (ICRU Report No 14 1969) The irradiated samples were measured with a NaI detector coupled to a pulse height analyser The full energy peak at 2 3 MeV was measured

For the investigated linear accelerators with accelerating voltages about 5 and 6 MV, the peak photon energy was controlled by comparing the ratio of the 5 cm and 15 cm depth doses with those determined from published depth dose data Ratios from published data are given in Fig 1 as a function of the peak photon energies The obtained curve may be uncertain because the accuracy of the peak energy determinations by the different laboratories or manufacturers are not known and because the depth dose curves are dependent on the flattening filters etc In ICRU Report No 14 (1969) it is stated, however, that the peak energy may be determined within 2 MV from published ratios (e g from Hospital Physicists Association (HPA), *1961, 1968*) From Fig 1 it can be seen *that the* ratios are most critical for low photon energies where the possibility of energy *determination by threshold analysis is lacking*

The energy calibration for electron beams was carried out by both threshold and range analysis The sample for threshold analysis was placed inside the col

Table 2

Practical extrapolated ranges R_p measured with different techniques — The estimated error in the determination of R_p was 0.1 cm

Electron energy E/MeV	Practical range R_p/cm extrapolated from		
	Depth dose* in H_2O	Depth ionization* in H_2O	Depth density** in polystyrene
13.3	6.65	6.63	6.70
23.4	11.93	11.90	11.78
27.7	14.15	14.10	14.07

* Measured with $FeSO_4$ in a 30 × 30 × 30 cm water phantom

** Measured with a small chamber in a 30 × 30 × 30 cm water phantom

*** Measured with photographic film in a polystyrene phantom

limator as close as possible to the scattering foil. The electron beam is always contaminated by roentgen rays produced in the tube window and in the scattering foil. These roentgen rays accounted for the whole or the major part of the induced radioactivity in the sample since their maximum photon energy was higher than the energy of the electrons hitting the sample. The mean energy loss of the electrons from collision losses in the tube window and scattering foil is for instance 1 to 2 MeV with a BBC 35 MeV betatron. Threshold analysis for electron radiation contaminated by roentgen rays thus gave an energy calibration which corresponded to the maximum energy of the contaminating roentgen rays. This latter, in turn, corresponded closely with the energy of the electrons leaving the acceleration orbit.

Energy range relations have been determined by several investigators using ionization chambers for the range measurements, previously by e.g. MARKUS (1964), ALMOND (1967), POHLIT (1969), NÜSSE (1969). The point where the extrapolation of the linear fall off of the depth ionization curves meet the roentgen ray background is usually called the practical range. In this investigation the practical range was measured from depth dose curves using $FeSO_4$ dosimeters and from depth ionization curves obtained with a thimble chamber in a water phantom and also from depth density curves obtained with film inside a special polystyrene phantom (HETTINGER & SVENSSON 1967). The effective measuring point with the thimble chambers was considered to be at a distance 3/4 r in front of the centre of the chamber, r being the radius of the chamber air cavity (HETTINGER et coll. 1967). Field sizes larger than 10 × 10 cm were used. Tests showed that the same practical range was obtained within 0.1 cm for a given MeV setting for the three techniques used (Table 2).

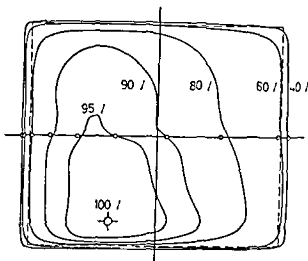


Fig. 2. Isodensity curves measured in laboratory No. 3 from a photographic film parallel to the phantom surface at a depth of 2 cm; field size 12 × 14 cm; e radiation 33 MeV. The electron beam was perpendicular to this plane. The ionization chamber checking points were normalized to the density per cent value at the central ray. The checking points at 95, 90, 80, 60 and 40 per cent relative ionization are shown. Ionization chamber ○ film density ——— geometrical field size — — —

Field size and beam flattening. Irradiations were performed with the beam perpendicularly incident upon the surface of a polystyrene phantom. Photographic films were used to measure the density distribution on a plane parallel to the surface. For electrons the depth of the observation plane was 2 cm, and for roentgen rays 5 cm. If the film (Kodak Microtex) was developed immediately after irradiation, the blackening was found to be proportional to the absorbed dose up to 3.2 O.D.U. This blackening was obtained at approximately 20 rad (in water). A Kodak A 3 developer was used, the developing time being 3.2 minutes at a temperature of 23.0° C. When developing was carried out 6 days after irradiation the degree of blackening was approximately 20 % lower but it was still proportional to the absorbed dose.

The films were developed in Umeå 5 to 6 days after the irradiations and scanned with an automatic isodensity plotter according to methods described by HETTINGER & SVENSSON (1967), and PETTERSSON (1967b).

The photographic film method was checked on all accelerators using thimble ionization chamber measurements in a water phantom. The thimble chamber was scanned in a plane perpendicular to the beam. The measuring depths were the same as those for the films. These checkings were carried out to investigate if the relative dose-picture with the short irradiations of the films — giving about 20 rad in dose maximum in water — were equal to the relative pictures from an irradiation time needed to give a patient dose (100 to 300 rad). One set of isodensity measurements and the ionization chamber checking points are shown in Fig. 2. With all the visited accelerators the agreement was about as good as the one shown in Fig. 2.

Source surface distance (SSD) The divergence of the beam was determined from the enlargement of a square formed by 4 thin wires (POHLIT 1965) The wire were placed on the normal treatment distance and were reproduced on a photographic film positioned 20 cm behind them

With roentgen rays the position of the focus was calculated from the diver gence The irradiations were carried out without flattening filters in the beams

Compared with roentgen rays electron beam depth doses show a minor depen dency of the virtual SSD (SCHULZ 1969) An accurate determination of SSD with electron radiation is therefore not so important as with roentgen rays With electron radiation the definition of the source is more complicated as tube window scattering foil and possible transmission chambers scatter the electrons It was however possible to measure a divergence as with roentgen rays even though the sharpness of the reproduced wires on the film was inferior In this paper the SSD was defined with electron radiation by the distance from the surface to the calculated virtual focus

Results and Discussion

Energy calibration of roentgen rays The peak energy data 5 and 6 MeV given by the manufacturers for the investigated linear accelerators agreed well with the energies estimated from comparisons between the measured ratios of 5 cm and 15 cm depth doses and published ratios (Fig 1)

Irrespective of whether photon or electron radiation was used the same calibra tion curves were obtained when the energy calibration of the MeV meter was carried out through threshold analysis The result could be predicted since the maximum photon energy for a certain MeV meter reading will be the same no matter whether the roentgen rays are produced in the target or whether the electrons are withdrawn and contaminating roentgen rays are produced in the accelerator window Consequently, for most of the betatrons threshold analysis was used only with roentgen rays

Energy calibration of electron radiation The electron energy at the phantom surface can be calculated by correcting for energy losses in the accelerator tube window the scatterer the transmission chamber and in the air NUSSE (1969) pointed out that in experimental determination of the energy range relationship these energy losses have often not been taken into account NUSSE (1969) estimated the total energy loss by summing up the collision and radiation losses Induced in Table 3 are all materials in the path of the electron beam of one of the BBC-betatrons (laboratory No 11) The energy loss however, has been calculated by considering only the collision losses These were between 2 3 and

Table 3

Estimated energy losses between accelerator tube and surface of the phantom — Laboratory No. 11 (BBC 35 MeV betatron)

Material	$\Delta x \cdot \varrho$	$\Delta x \cdot \varrho \cdot \frac{S_{coll}}{\varrho}$ (15 MeV)	$\Delta x \cdot \varrho \cdot \frac{S_{coll}}{\varrho}$ (30 MeV)	Estimated error
Tube window	0.38 g/cm²	0.65 MeV	0.68 MeV	±0.1 MeV
Scatterer 1	0.27 g/cm²	0.40 MeV		±0.1 MeV
2	0.36 g/cm²		0.56 MeV	
Monitors	0.52 g/cm²	0.99 MeV	1.02 MeV	±0.1 MeV
Air (103 cm)	0.13 g/cm²	0.25 MeV	0.29 MeV	
	Σ	2.3 MeV	2.6 MeV	±0.2 MeV

2.6 MeV in the energy range 15 to 30 MeV. The reason for considering collision losses alone was that only a few per cent of the primary electrons experienced radiation loss on travelling through the material between the tube and the phantom. The energy loss is, however, on the other hand, on an average much greater through one radiation than through one collision process. Electrons which have lost a large portion of their initial energy are more likely to be scattered away from the radiation beam than other primary electrons.

Fig. 3, curve (a), shows the results obtained by calibrating the MeV meter of one of the BBC betatrons (laboratory No. 11) using threshold analysis. The energy of the electrons immediately before passing the accelerator window was determined. The energy, E_o (MeV), at the phantom surface, curve (b), was calculated by subtracting the energy loss arising from collision losses, 2.3 and 2.6 MeV at 15 and 30 MeV, respectively, according to Table 3. The practical range, R_p (cm), was determined at different MeV meter settings — between about 10 to 30 MeV — as previously described. If the energy calibration according to Fig. 3, curve (b), were supposed to be correct, the following energy-range relation and standard errors (14 measurements of R_p) were obtained:

$$R_p = k_1 \cdot E_o - k_2$$

where

$k_1 = 0.520 \pm 0.003 \text{ MeV}^{-1} \text{ cm}$

$k_2 = 0.26 \pm 0.08 \text{ cm}$

The *energy range relation* was also determined with a Siemens 42 MeV betatron. The energy loss from accelerator window to the phantom arising from

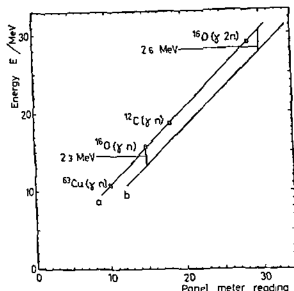


Fig 3 Curve (a) Energy calibration of the MeV meter at electron radiation using threshold analysis in laboratory No 11 The energy of the electrons immediately before passing the accelerator window was determined Curve (b) The energy at the phantom surface calculated by subtracting the energy loss arising from collision losses according to Table 2 This curve was correlated to the practical ranges measured with several MeV meter settings the coefficients k_1 and k_2 in the equation (p 000) were determined

collision losses was only 0 4 MeV at an electron energy of 15 MeV (The scattering foils used at this energy for radiotherapy in order to flatten large field sizes gave collision losses between 1 0 and 1 7 MeV) The energy range relation determined with this betatron agreed closely with the equation

The difference between the energy at the accelerator window (determined by (γ n) analysis) and the energy at the phantom surface (determined from range analysis using the equation) was 2 0 to 2 6 MeV at 15 MeV for 8 other BBC betatrons Data from the manufacturer show that the material in the path of the beam causes corresponding energy losses

The measurements of R_p were made at SSD 103 cm with the BBC betatron and at SSD 102 cm with the Siemens 42 MeV betatron Correction of the depth dose curves to infinite SSD as suggested by NÜSSE (1969) increases R_p about 0 1 cm at 30 MeV and with smaller values at lower energies Since most accelerators used in the Nordic countries employ SSD of about 100 cm this correction has not been made

The systematic errors in E and R_p are not included in the errors given in the equation The uncertainty in E arises due to difficulties in measuring the thresholds ($\approx$ 0 1 MeV) uncertainty in absolute values of the threshold energies ($\approx$ 0 5 % ICRU Report No 14 1969) and in calculating the collision losses ($\approx$ 0 2 MeV) The systematic error in R_p (Table 2) has been estimated to 0 1 cm which corresponds to an uncertainty in E_o equal to about 0 2 MeV The

Table 3

Estimated energy losses between accelerator tube and surface of the phantom — Laboratory No. 11 (BBC 35 MeV betatron)

Material	$\Delta x \cdot \varrho$	$\Delta x \cdot \varrho \cdot \frac{S_{coll}}{\varrho}$ (15 MeV)	$\Delta x \cdot \varrho \cdot \frac{S_{coll}}{\varrho}$ (30 MeV)	Estimated error
Tube window	0.38 g/cm²	0.65 MeV	0.68 MeV	±0.1 MeV
Scatterer 1	0.27 g/cm²	0.40 MeV		
				±0.1 MeV
2	0.36 g/cm²		0.56 MeV	
Monitors	0.52 g/cm²	0.99 MeV	1.02 MeV	
				±0.1 MeV
Air (103 cm)	0.13 g/cm²	0.25 MeV	0.29 MeV	
	Σ	2.3 MeV	2.6 MeV	±0.2 MeV

2.6 MeV in the energy range 15 to 30 MeV. The reason for considering collision losses alone was that only a few per cent of the primary electrons experienced radiation loss on travelling through the material between the tube and the phantom. The energy loss is, however, on the other hand, on an average much greater through one radiation than through one collision process. Electrons which have lost a large portion of their initial energy are more likely to be scattered away from the radiation beam than other primary electrons.

Fig. 3, curve (a), shows the results obtained by calibrating the MeV meter of one of the BBC betatrons (laboratory No. 11) using threshold analysis. The energy of the electrons immediately before passing the accelerator window was determined. The energy, E_o (MeV), at the phantom surface, curve (b), was calculated by subtracting the energy loss arising from collision losses 2.3 and 2.6 MeV at 15 and 30 MeV respectively according to Table 3. The practical range, R_p (cm), was determined at different MeV meter settings — between about 10 to 30 MeV — as previously described. If the energy calibration according to Fig. 3, curve (b) were supposed to be correct, the following energy range relation and standard errors (14 measurements of R_p) were obtained

$$R_p = k_1 \cdot E_o - k_2$$

where

$k_1 = 0.520 \pm 0.003\ \mathrm{MeV}^{-1}\ \mathrm{cm}$

$k_2 = 0.26 \pm 0.08\ \mathrm{cm}$

The energy range relation was also determined with a Siemens 42 MeV betatron. The energy loss from accelerator window to the phantom arising from

Table 5

Average homogeneity indices for e radiation — Depth 2 cm H_2O Field size S (10 to 200 cm^2)

Laboratory number	9 to 20 MeV		25 to 35 MeV	
	Area (90)/S	Area (80)/S	Area (90)/S	Area (80)/S
1	0 68 (5)	0 83 (5)	0 48 (2)	0 81 (2)
2	0 35 (5)	0 57 (5)	0 46 (10)	0 67 (10)
3	0 36 (5)	0 63 (5)	0 37 (9)	0 67 (9)
4	0 40 (9)	0 62 (9)	0 64 (8)	0 82 (8)
5	0 36 (5)	0 62 (5)	0 44 (7)	0 76 (7)
6	0 40 (6)	0 64 (6)	0 49 (7)	0 76 (7)
7	0 28 (5)	0 55 (5)	0 51 (6)	0 71 (6)
8	0 26 (6)	0 48 (6)	0 40 (9)	0 65 (9)
9	0 57 (5)	0 78 (5)		
10	0 82 (2)	0 90 (2)	0 80 (8)	0 94 (8)
11	0 67 (6)	0 80 (6)	0 78 (4)	0 93 (4)

quoted are average values of several measurements using two different energy ranges Values within parentheses give the combinations of field sizes and electron energies employed with each accelerator The relative standard deviations of the ratios were generally less than 4 % Corresponding measurements were also carried out with roentgen rays All irradiations were performed using scatterers or flattening systems which provided optimum flattening both with electron and roentgen radiation The density in the central beam was often considerably — up to about 10 % — lower than the maximum density Even when different radiotherapy centres perform accurate calibrations in the central axis the maximum absorbed dose to the patient can therefore vary depending upon different homogeneity Treatment planning does not always eliminate this difference since isodose curves are often measured on a plane parallel with the beam direction This plane does not necessarily go through the point which contains the absolute absorbed dose maximum

In Fig 2 the 90 % curve covers an area which is only 38 % of the geometrical field area the 80 % curve covers an area which is 69 % of the field area The geometrical field area was taken as that defined by the collimator or by the light field on the phantom surface These figures are measures of the flattening and have in this paper been defined as homogeneity indices Table 5 shows average values of the homogeneity indices for electron beams with different accelerators The standard deviations of the indices given in Table 5 were in general somewhat less than 0 1 The 90 % curve in most cases covered less than half the

Table 4

The ratio between the density on the central axis at 2 cm depth and the maximum density at this depth. — The number of combinations of field sizes and energies investigated are given within parentheses

Laboratory number	e^- radiation	
	9 to 20 MeV	25 to 35 MeV
1	0.97 (6)	0.98 (2)
2	0.98 (5)	0.96 (10)
3	0.98 (5)	0.95 (9)
4	0.99 (9)	0.99 (8)
5	0.98 (5)	0.96 (7)
6	0.96 (6)	0.94 (7)
7	0.95 (5)	0.96 (6)
8	0.97 (6)	0.97 (9)
9	0.97 (5)	
10	0.96 (2)	0.95 (9)
11	0.99 (6)	0.99 (4)

over all uncertainty in E_o calculated from the arithmetic sum of the separate uncertainty plus standard error multiplied by t factor for 95 % confidence level (ICRU Report No. 12) equals to ± 0.8 MeV.

The energy range relation or threshold analysis with corrections for collision losses can be used only to provide an estimate of the primary electrons maximum energy at the phantom surface. The average energy of the primary electrons at the phantom surface, on the other hand, depends upon the collision and radiation losses, energy degradation in the collimator, rejection of low energy electrons by the magnetic field outside the accelerator orbit, etc. There is no simple method for determining the average energy. If, however, the energy range relation is used in a uniform way by different centres to determine E_o it is possible to transfer absorbed dose calibrations with thimble chambers with an uncertainty less than 2 % (SVENSSON 1971a).

The values of k_1 and k, in the equation agree with the factors recommended by SCRAD (1966), which are mean values from different investigators. This equation ought therefore to be possible to use by different centres to give the uniformity.

Field size and beam flattening. The maximum density on the photographic films, taken for the checking of beam flattening, was mostly situated outside the central axis (Fig. 2). The ratio between the density on the central axis and the maximum density was determined for electron radiation (Table 4). The ratios

aperture could be varied to provide a given field size ≤ 17.5 cm (SVENSSON & HETTINGER 1967). With these two betatrons the homogeneity indices increased by about 50 %. In laboratory No. 4 a similar collimator was employed for some field sizes, the average value of the homogeneity index consequently increased for this laboratory too. This type of collimator has now been further improved in laboratory No. 11. The transmission dose monitor was replaced with a monitor system outside the central beam to minimize the scattering and energy degradation of the electrons. A light field on the patient surface indicates the geometrical field size. The 90 % isodensity curve covers almost the whole of the geometrical field area with all field sizes smaller than ⌀ 19 cm. This investigation shows that it is possible to make homogeneous fields with electron radiation (SVENSSON 1971b).

The flattening of photon radiation is given in Table 6. Measurements were performed using only one field size. The flattening of photon radiation was decidedly better than that of electron beams. The best flattening was obtained with 5 to 6 MV linear accelerators.

SCRAD (1966) recommended that the field size be defined by the dimensions of the plane figure described by the intersection of the 90 % isodose surface with the plane passing through, and normal to, the central axis at the position of the relative dose maximum which is normalized to 100 %. This definition of field size was inapplicable to the majority of the betatrons investigated for both electron and photon radiation since, according to Tables 5 and 6, the flattening was too poor. The 90 % isodose surfaces describe irregular figures and depth dose curves cannot in a meaningful way be correlated to these figures.

SSD determination was made for 6 of the BBC betatrons. An experimentally determined SSD of 103 ± 2 (standard deviation) cm for electron radiation may be compared with a value of 110 cm provided by the manufacturer. The measured distance is equal to that from the window of the accelerator tube to the edge of the collimator facing the phantom. For roentgen rays an SSD of 101 ± 3 cm may be compared with 100 cm given. The SSD approximately corresponded to the distance between the target and the surface.

Using a Siemens 42 MeV betatron, SSD's for electron and roentgen radiation were found to be 102 cm and 105 cm, respectively. The manufacturer's figures were 100 cm in both cases.

Conclusions

(1) The methods employed for energy calibration, that is, threshold analysis and range analysis, gave consistent results with the 11 betatrons. A uniform energy calibration of betatron radiation is thus possible.

Table 6

Homogeneity indices for roentgen rays — Depth 5 cm H_2O

Laboratory number	Rtg rays	Field size S (cm²)	Area (90 %)/S	Area (80 %)/S
1	40 MV	12×12	0 26	0 63
2	32 MV	8×8	0 61	0 83
3	33 MV	16×16	0 69	0 93
4	32 MV	16×16	0 72	0 95
	5 MV	10×10	0 72	0 89
5	32 MV	16×16	0 63	0 89
6	31 MV	16×16	0 78	0 98
7	32 MV	16×16	0 74	0 96
	6 MV	10×10	0 78	1 00
		20×20	0 78	0 98
8	33 MV	16×16	0 74	0 95
9	17 MV	7×8	0 60	0 94
	6 MV	6×6	0 78	0 96
		10×10	0 86	1 00
		20×20	0 94	1 00
10	34 MV	10×10	0 85	0 98
11	34 MV	8×8	0 73	0 94

geometrical field area The values using the higher energies were often better than with the lower

On a BBC betatron the flattening of the electron beam depends partly upon the settings on the betatron s control panel, where the direction of the central beam in the plane of the accelerator tube can be influenced, and partly upon the scattering and collimator systems Seven out of nine laboratories with BBC betatrons had added to them a balancing chamber which indicated small changes in the direction of the central axis of the radiation beam The operator was thereby able to adjust the beam field from the control panel (PETTERSSON & HETTINGER 1965, VON ARX 1965, ROBINSON & McDOUGALL 1967) The poor flattening of energies above 25 MeV in laboratory No 3 (Table 5) arose from the absence of a balancing chamber

BBC betatrons are delivered with plexiglas tubes for limiting the beam Owing to electron scattering in the tube walls, the dose at the edges of the geometrical field was considerably lower than at the field centre This is one reason for the poor flattening shown in Table 5 On two of the betatrons in laboratories No 10 and 11, the plexiglas tubes had been replaced by a metal plate positioned as near the patient as possible There was a circular hole in the centre of the plate The

RÉSUMÉ

Les auteurs ont execute un programme de mesures sur des bétatrons et des accelerateurs lineaires dans onze laboratoires situes au Danemark, en Finlande en Norvege et en Suede Il ont montré qu on peut utiliser un équipement simple pour determiner l energie la pla neite et la distance source peau d une façon uniforme avec les differents accelerateurs Ils proposent un u de d homogeneite pour definir la planeite du faisceau

REFERENCES

ALMOND P R The physical measurements of electron beams from 6 to 18 MeV Absorbed dose and energy calibra ion Phys in Med Biol 12 (1967) 13

VON ARX A Continuous or periodical control of field homogeneity *In* Symposium on high energy electrons p 85 Edited by A Zuppinger and G Poretti Springer Verlag Berlin 1965

EHRLICH M and LAMPERTI P J Uniformity of high-energy electron beam calibrations Phys in Med Biol 14 (1969) 305

GREENE D The HPA and AAPM survey of depth-dose data for teleisotope γ rays and mega voltage X rays *In* High energy radiation therapy dosimetry Edited by J S Laughlin Ann N Y Acad Sci 161 (1969) 168

HETTINGER G and SVENSSON H Photographic film for determination of isodose curves from betatron electron radiation Acta radiol Ther Phys Biol 6 (1967) 74

— PETTERSSON C and SVENSSON H Displacement effect of thimble chambers exposed to a photon or electron beam from a betatron Acta radiol Ther Phys Biol 6 (1967) 61

HOLT J G ALMOND P R and MELRK M L Intercomparison and calibration of high energy X rays and electrons *In* High energy radiation therapy dosimetry Edited by J S Laughlin Ann N Y Acad Sci 161 (1969) 133

HOSPITAL PHYSICISTS ASSOCIATION (HPA) Depth dose tables for use in radiotherapy Brit J Radiol Suppl 10 *(1961)*

— A review of Suppl No 10 Depth dose tables for use in radiotherapy Brit J Radiol 41 *(1968) 932*

INTERNATIONAL COMMISSION ON RADIATION UNITS AND MEASUREMENTS (ICRU) Report No 10d Clinical dosimetry National Bureau of Standards Handbook 87 NBS Washington 1963

— Report No 12 *Certification of standardized* radioactive sources ICRU Washington 1968

— Report No 14 Radiation dosimetry X rays and gamma rays with maximum photon energies between 0 6 and 50 MeV ICRU Washington 1969

LOEVINGER R PFALZNER P M EISENLOHR H et coll The IAEA program in medical radiation dosimetry *In* High energy radiation therapy dosimetry Edited by J S Laughlin Ann N Y Acad Sci 161 (1969) 158

MARKUS B Beitrage zur Entwicklung der Dosimetrie schneller Elektronen Teil II Strahlentherapie 123 (1964) 508

NÜSSE M Factors affecting the energy range relation of fast electrons in aluminium Phys in Med Biol 14 (1969) 315

PETTERSSON C (a) Absolute and relative radiation dosimetry at a 35 MeV medical betatron The Department of radiation therapy and physics University of Umeå 1967

— (b Automatic isodensity recorder for photographic dosimetry Acta radiol Ther Phys Biol 6 (1967) 225

(2) Dose maximum lies outside the central axis for most of the beams used from the 11 investigated betatrons Even when the different centres have uniform absorbed dose calibrations in the central axis the maximum dose to the patient may thus differ as much as 10 %

(3) With most of the betatrons the flattening was remarkably bad The degree of inhomogeneity which can be tolerated in radiation therapy need to be investigated A homogeneity index, defined in this paper, may be used to describe the flattening The description of field size should include both the geometrical size and the homogeneity index The manufacturers of betatrons ought to improve the scattering foils and collimating systems so that better flattening is obtained

(4) Simple measuring equipment could be used to measure energy, the point of dose maximum outside the central ray, flattening, and SSD If these characteristics of the beams are determined by the different laboratories, more uniform absorbed dose calibrations ought to be possible to perform, depth dose and isodose curves from the different laboratories ought to be possible to compare in a more meaningful way (SVENSSON 1971a)

Acknowledgements

The authors gratefully acknowledge the radiotherapeuts and physicists at the visited places and the technical assistance of Mr B Sjostrom The work was supported by grants from the Swedish Cancer Society

SUMMARY

A measuring program was carried out at betatrons and linear accelerators at 11 laboratories in Denmark Finland Norway and Sweden It was shown that simple equipment could be used to determine energy flattening and SSD in a uniform way with the different accelerators In order to describe the beam flattening a proposal was given for a homogeneity index

ZUSAMMENFASSUNG

Ein Messprogramm fur Elektronenschleudern und Linearacceleratoren von 11 Laboratorien in Danemark Finland Norwegen und Schweden wurde durchgefuhrt Es wird gezeigt dass eine einfache Ausrustung verwendet werden kann um die Energie die Abflachung und die SSD in gleichmassiger Weise bei den verschiedenen Acceleratoren zu bestimmen Um die Strahlenabflachung zu beschreiben wird ein Vorschlag fur einen Homogenitatsindex gemacht

ACTA RADIOLOGICA
OFFICIAL ORGAN OF THE RADIOLOGICAL SOCIETIES OF
DENMARK FINLAND NORWAY AND SWEDEN

Vol 10 Fasc 4 THERAPY PHYSICS BIOLOGY 1971 August

INVESTIGATION ON TUMOUR SPREAD IN CONNECTION WITH ASPIRATION BIOPSY

by

U ENGZELL P L ESPOSTI C RUBIO A SIGURDSON and J ZAJICEK

Fine needle aspiration biopsy has been used for many decades in the diagnosis of malignancy in various organs The method is relatively atraumatic and there appear to be no definite contraindications to its use in lesions accessible to puncture (MARTIN & ELLIS 1930 1934, MARTIN & STEWART 1936 SODERSTROM 1966)

One conceivable complication of aspiration biopsy of neoplastic tissue is the dissemination of tumour cells or cell clusters through the needle track or through efferent lymph or blood vessels resulting in extension of tumour growth and a poorer prognosis (MARTIN & STEWART 1936 ROBBINS et coll 1954 BANGLE 1961 BERG & ROBBINS 1962 SODERSTROM 1966)

In order to investigate if aspiration biopsy with the digital manipulation it involves can produce spread of tumour cells by efferent lymphatics or blood vessels or through the needle track investigations were made on rabbits with popliteal lymph node metastases from Vx2 carcinoma inoculated into the hind

From the Departments of Otolaryngology of Oral and Jaw Diseases and of Clinical Cytology Institute of Tumour Pathology Karolinska Sjukhuset Stockholm Sweden This investigation was supported by grants from The Swedish Cancer Society (Nos 69 147 and 70 175 and The Cancer Society of Stockholm Submitted for publication 15 January 1971

— HETTINGER G A balancing chamber for stabilizing the homogeneity of the electron field between 10 and 35 MeV *In* Symposium on high energy electrons p 89 Edited by A Zuppinger and G Poretti Springer Verlag Berlin 1965

POHLIT W Dosimetrie zur Betatrontherapie Georg Thieme Verlag Stuttgart 1965

— Energy calibration of betatron X rays and electrons up to 40 MeV *In* High energy radiation therapy dosimetry Edited by J S Laughlin Ann N Y Acad Sci 161 (1969), 119

ROBINSON J E and MCDOUGALL R S Electron beam instability and isodose asymmetry associated with a 35 MeV medical betatron Phys in Med Biol 12 (1967) 315

SCHULZ R J AAPM/HPA survey of high energy electron depth dose data *In* High energy radiation therapy dosimetry Edited by J S Laughlin Ann N Y Acad Sci 161 (1969) 176

SUB COMMITTEE ON RADIATION DOSIMETRY (SCRAD) OF THE AMERICAN ASSOCIATION OF PHYSICISTS IN MEDICINE Protocol for the dosimetry of high energy electrons. Phys in Med Biol 11 (1966) 505

SVENSSON H (a) Dosimetric measurements at the Nordic medical accelerators II Absorbed dose measurements To be published in Acta radiol Ther Phys Biol 10 (1971)

— (b) The influence of scattering foils transmission monitors and collimating system on the absorbed dose distribution from 10 to 35 MeV electron radiation To be published in Acta radiol Ther Phys Biol 10 (1971)

— and HETTINGER G *Influence of collimating systems on dose distribution from 10 to 35 MeV electron radiation* Acta radiol Ther Phys Biol 6 (1967) 404

WEBSTER E W and TSIEN K C Atlas of radiation dose distributions Vol I Single field isodose charts IAEA Vienna 1965



Fig 1 Lymphogram sho ing the inserted poly thene catheter in the efferent lymphatic of a popliteal lymph node in a rabbit

before the needle was withdrawn from the node During and after the needling, 0 5 ml of lymph was collected with the aid of passive leg movements

In order to collect blood leaving the node the efferent vein was di ected free and a polythene catheter (PE 50) was introduced directly or via the femoral vein and fixed with a ligature To counteract clotting 0 5 ml heparin (Vitrum 5 000 IU/ml) was injected intravenously immediately before the cannulation

From this catheter 1 ml of blood was collected with the leg at rest 1 ml during gentle massage of the lymph node and 1 ml during and after aspiration biopsy of the node The samples of efferent lymph and blood were collected in siliconized test tubes containing one drop of sodium citrate

Tumour cell pread through the perforations made by needling the capsule was investigated as follows After the aspiration biopsy the lymph node was gripped between finger and thumb and fluid material which then appeared out ide the capsule in the region of the puncture was collected by scraping with a thick coverslip (such as used in a Burker counting chamber) The material was depo ited on a precleaned glass slide and spread with the aid of the cover slip

The lymph node was extirpated and fixed in 9 per cent formalin olution for further histologic examination

The amples of lymph and blood were edimented in a refrigerated centrifuge at 1 000 G for 7 minutes The lymph and plasma were then pipetted off and the

paw The efferent lymph and blood were analyzed for presence of carcinoma cells before and after aspiration biopsy Fluid escaping through the needle perforations in the capsule of the metastasis bearing node was likewise analyzed for tumour cells

As a clinical approach to the question of needle track dissemination of neoplastic cells, the records of 157 patients with pleomorphic adenoma of the major salivary glands and of 469 patients with prostatic carcinoma were reviewed The primary diagnosis had been obtained by fine needle biopsy

Material and Methods

Experimental investigation

Full grown domestic rabbits of both sexes were inoculated in the tarsal region of one hind leg with a suspension of transplantable Vx2 carcinoma cells and cell clusters About two weeks later an enlarged lymph node could be palpated in the popliteal fossa of the same leg The experiments on lymph nodes were performed 11 to 35 days after the inoculation with the carcinoma suspension

The rabbits were anaesthetized via a polythene catheter (PE 50, Clay Adams Co Inc) inserted into a marginal ear vein Veterinary nembutal (Abbott 60 mg/ml) diluted 1 5 in 0 9 per cent saline solution was used By leaving the catheter in position throughout the experiment, maintenance doses could be given as required

The lateral part of the hind leg was shaved and cleaned An incision was made through the skin and muscles proximal to the popliteal fossa and the lateral aspect of the lymph node was explored without damaging the node capsule To collect the lymph leaving the node, the efferent lymphatic vessel was dissected free and a polythene catheter (PE 50) was introduced and fixed with a ligature (Fig 1) The catheter was kept in position by a small cuff at the tip made by heating over a flame (TJERNBERG 1962) The cannulations were performed under a Zeiss dissection microscope with 6 to 16 × magnification

During lymph sampling the rabbit's hind leg was cautiously subjected to passive movements, to obtain an adequate flow of lymph through the catheter into a test tube After 15 to 20 minutes, 0 5 ml of efferent lymph had been collected The effect of digital manipulation in regard to tumour cell spread was then investigated by gently massaging the node between finger and thumb for 5 to 10 minutes until 0 5 ml of lymph had been collected The massage was followed by aspiration biopsy, using an 18 gauge needle The needle was introduced into the node in different directions three to four times under simultaneous aspiration The aspiration was discontinued by releasing the piston

Table

Vx2 carcinoma cells in lymph and blood leaving histologically verified popliteal lymph node metastases and at the sites of capsular puncture for aspiration biopsy of the nodes. Experiments on rabbits

Analysis of	No. of experiments	Carcinoma cells in efferent fluid			Carcinoma cells at puncture sites
		Before massage of node	At massage of node	At aspiration biopsy	
Efferent lymph	7	—	1*	1*	
Efferent blood	9	—	1**	1**	
Puncture site smear	1?				10

* = same rabbit
** = same rabbit

Prostatic carcinomas. Hormonal therapy alone was given in 469 patients with carcinoma of the prostate diagnosed by transrectal aspiration biopsy from 1956 through 1965 (Esposti 1971). Regular follow up including rectal palpation was made one, three, six and twelve months from the start of treatment and thereafter at least once yearly. All the patients were clinically followed up until death or for at least five years.

For the transrectal aspiration biopsies, the technique described by Franzen et coll. (1960) was used. A 22 gauge, 20 cm long, flexible needle was guided through a fine curved metal tube having at its distal end a metal ring to be threaded over the operator's left index finger (Fig. 2). The needle could be introduced into any prostatic focus during digital palpation of the gland.

Results

Experimental investigation

Aspiration biopsy of popliteal lymph nodes with simultaneous collection of efferent lymph or blood was performed on 21 rabbits previously inoculated with Vx2 carcinoma. The efferent lymphatic was cannulated in 10 experiments and the efferent vein in 11. Subsequent histologic examination of the lymph nodes revealed carcinoma in 16 rabbits. The other five rabbits, in which carcinoma was not found, were withdrawn from the investigation.

The results of the cytologic analyses in these 16 rabbits are summarized in the Table. Immediately after cannulation of lymphatics or blood vessels, no carcinoma cells were found in the collected lymph or blood. In the lymph collected

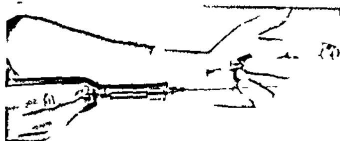


Fig 2 Instrument for transrectal aspiration biopsy The needle guide is threaded over the left index finger and the syringe with a 22 gauge needle is held by the right hand

sedimented cells were washed twice in Hanks' solution The cells were resuspended in a few drops of Hanks' solution and fixed in methanol glacial acetic acid mixture in a proportion of 10 1 For lymph cells, 5 ml of fixative was used and for blood cells 10 ml The fixed cells were thereafter sedimented by centrifugation, resuspended in 5 and 10 ml of fixative, respectively, and stored overnight

These cell suspensions were centrifuged and the sediment was transferred to clean slides The emptied tubes were rinsed with a drop of 1 per cent pectin solution, which was then distributed over the material on the slides The pectin was used to increase cell adhesion to the slides (ROFF 1955) The slides were allowed to dry overnight They were then stained with Harris haematoxylin for one minute and mounted with Eukitt synthetic resin

The smears obtained by scraping the capsule at the site of needling were fixed in methanol acetic acid mixture and stained with haematoxylin Air dried smears were also prepared, using May Grunwald Giemsa stain

The slides were screened for carcinoma cells under a Zeiss microscope (400 ×) Possible malignant cells were viewed under oil immersion (1 000 ×) Only unmistakable carcinoma cells and cell plugs were recorded

Clinical investigation

Pleomorphic adenomas From 1955 through 1960 157 pleomorphic adenomas of the major salivary glands were primarily diagnosed by aspiration biopsy All patients were subsequently operated upon, but special care was not taken to extirpate the biopsy needle tracks One hundred and five of these patients received radiotherapy, as a rule 3 000 rad, between aspiration biopsy and operation A ten year follow up was made by reviewing the clinical records Patients with insufficiently long clinical observation periods were interviewed after ten years or more

A 22 gauge needle was used for the biopsy in all these patients The needle was attached to a syringe fitted with a special one hand grip (FRANZEN et coll 1960)

Table

Vx2 carcinoma cells in lymph and blood leaving histologically verified popliteal lymph node metastases and at the sites of capsular puncture for aspiration biopsy of the nodes. Experiments on rabbits

Analysis of	No of experiments	Carcinoma cells in efferent fluid			Carcinoma cells at puncture sites
		Before massage of node	At massage of node	At aspiration biopsy	
Efferent lymph	7	—	1	1*	
Efferent blood	9	—	1*	1*	
Puncture site smear	12				10

= same rabbit
* = same rabbit

Prostatic carcinomas. Hormonal therapy alone was given in 469 patients with carcinoma of the prostate diagnosed by transrectal aspiration biopsy from 1956 through 1965 (ESPOSTI 1971). Regular follow up including rectal palpation was made one, three, six and twelve months from the start of treatment and thereafter at least once yearly. All the patients were clinically followed up until death or for at least five years.

For the transrectal aspiration biopsies the technique described by FRANZEN et coll. (1960) was used. A 22 gauge, 20 cm long, flexible needle was guided through a fine curved metal tube having at its distal end a metal ring to be threaded over the operator's left index finger (Fig. 2). The needle could be introduced into any prostatic focus during digital palpation of the gland.

Results

Experimental investigation

Aspiration biopsy of popliteal lymph nodes with simultaneous collection of efferent lymph or blood was performed on 21 rabbits previously inoculated with Vx2 carcinoma. The efferent lymphatic was cannulated in 10 experiments and the efferent vein in 11. Subsequent histologic examination of the lymph nodes revealed carcinoma in 16 rabbits. The other five rabbits in which carcinoma was not found were withdrawn from the investigation.

The results of the cytologic analyses in these 16 rabbits are summarized in the Table. Immediately after cannulation of lymphatics or blood vessels no carcinoma cells were found in the collected lymph or blood. In the lymph collected

during gentle massage of the metastatic node before aspiration biopsy, carcinoma cells were found in one of seven rabbits The same rabbit had carcinoma cells in the lymph collected during and after the needling In the remaining six rabbits, no carcinoma cells were found in the efferent lymph In all seven experiments the lymph collected during and after aspiration biopsy was blood stained and contained variable amounts of erythrocytes

The blood leaving the metastatic node was analyzed in nine rabbits (cf Table) Tumour cells were *found in the sample collected from one rabbit during* massage before the aspiration biopsy, and in the same rabbit in the sample collected during and after biopsy No carcinoma cells were found in the blood from the remaining eight rabbits

The fluid material which escaped through the needle punctures in the lymph node capsule was cytologically analyzed in 12 experiments Carcinoma cells were then demonstrated in ten rabbits (cf Table) The biopsy aspirate contained carcinoma cells in these ten rabbits, but was negative for such cells in the other two

Clinical investigation

Pleomorphic adenomas In the ten year follow up of 157 patients in whom aspiration biopsy had revealed pleomorphic adenoma of the major salivary glands *ten patients could not be traced Of the remaining 147 patients*, 23 had died from other causes without known recurrence of the salivary gland tumour Of the 124 patients who were still alive, 97 had been clinically observed for at *least ten years, and the other 27 were interviewed after ten years or more* In 121 cases there had been no recurrence of the tumour The three patients with local recurrence of the pleomorphic adenoma underwent secondary operation four, *five and nine years, respectively, after the initial operation* Review of the records showed that in two of these three patients the primary extirpation had not been radical In no case was there any sign at the secondary operation of *tumour growth subcutaneously or cutaneously*, i e in the region of the needle track

Prostatic carcinomas In four of the 469 patients with carcinoma of the prostate, there was an exophytically growing tumour bulging into the rectum at the time of the needle biopsy The five year follow up revealed that ten patients died less than a month after treatment was instituted and consequently were not clinically re examined Autopsy was performed in three of the cases and diffuse metastases from poorly differentiated prostatic carcinoma without sign of tumour growth through the prostato rectal fascia and the rectal wall were found Of the remaining 459 patients, 400 were alive after one year, 279 after three

years and 242 after five years Scrutiny of the examining urologists reports on the findings at regularly repeated palpatory follow up indicated that transrectal tumour growth occurred in one patient three years after the needling In the other 458 patients there were no signs of tumour invasion of the prostato-rectal fascia and the rectal wall

The patient with rectal involvement had a poorly differentiated carcinoma, which was locally advanced and with induration extending beyond the capsule of the prostate Regression of the tumour occurred shortly after treatment was begun and a repeat aspiration biopsy after two months revealed a moderately good cytologic response (ESPOSTI 1971) Three years later rapid progression took place and at the end of that year a large rectal tumour extending almost to the external anal orifice could be palpated The patient died with generalized metastases four years after the start of treatment

Discussion

Little has been written concerning the possibility that tumour cells or cell clusters can spread locally along the needle track or distantly via the lymphatics or blood vessels in connection with aspiration biopsy of neoplastic lesions and thus result in metastatic growth

Tumour growth along the tracks of needles used for biopsy of palpable tumours has occasionally been reported CRILE & HAZARD (1951) described a case of papillary carcinoma of the thyroid in which a Silverman needle was used to obtain material for tissue section Surgery was not performed One year later tumour growth was found in the skin where the needle had been introduced

ACKERMAN & WHEAT (1955) reported a case of squamous carcinoma and one of malignant melanoma in which tumour growth could be demonstrated along the needle track 16 and 9 days respectively after aspiration biopsy of the lesion The size and type of needle were not stated

In four cases of carcinoma of the prostate local tumour extension was attributed to transperineal thick needle biopsy performed 6 to 13 months previously (CLARKE et coll 1953 GOLDMAN & SAMELLAS 1960 BURKHOLDER & KAUFMAN 1966 LABARDINI & NESBIT 1967)

Dissemination of malignant cells along the needle track was observed by CACIUN et coll (1969) following aspiration of a lymph node metastasis of the neck The size of the needle was not specified

A search of the literature has revealed no definite reports of local tumour extension caused by fine needle (18—22 gauge) aspiration biopsy

In the present investigation aspiration biopsy of lymph node metastases from Vx2 carcinoma was performed in rabbits When the aspirate contained carci

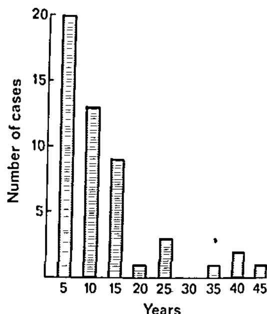


Fig. 3. Time lapse from the treatment of original tumour to the diagnosis of local recurrence in 50 patients with recurrent pleomorphic adenoma of the parotid gland.

noma cells; such cells were found also outside the capsule of the node at the sites of puncture. This suggests that tumour cells may escape through the capsular perforations caused by fine needle biopsy of an encapsulated tumour and may spread along the needle track. ZAJICEK (1970) observed that blood escaping through the needle track after aspiration biopsy of mammary carcinoma could contain tumour cells.

The clinical significance of these observations is difficult to evaluate, as most malignant tumours, the area of needling included, are subjected to subsequent therapeutic measures such as surgical excision or radiotherapy. In a previous five year follow up of 656 patients with cervical lymph node metastases diagnosed by aspiration biopsy, there was no clinical evidence of local tumour growth resulting from the biopsy (ENGZELL et coll. 1971).

The clinical part of the present investigation comprised follow up of patients with pleomorphic adenoma of the major salivary glands or carcinoma of the prostate. All the tumours had been diagnosed by aspiration biopsy. In these tumour types it seems reasonable to assume that spread of neoplastic cells resulting in tumour growth along the needle track would be revealed during clinical follow up.

The incidence of postoperative recurrence of pleomorphic adenomas of the major salivary glands has been reported as varying from 0 to almost 50 per cent (AHLBOM 1935, MCFARLAND 1942, BUXTON et coll. 1953, EDVALL 1954, IRA

ZELL 1954 BEAHRS et coll 1960 GRAGE et coll 1961) It has been stated that a high postoperative recurrence rate must be ascribed to insufficient removal of salivary gland tissue leaving small tumour excrescences (BEAHRS et coll 1960 GRAGE et coll 1961, ENEROTH 1964)

In our experience most recurrences appear within ten years of the removal of the original tumour Of 50 recurrent pleomorphic adenomas treated at Karolinska Sjukhuset between 1955 and 1965 33 (66 per cent) appeared within ten years of the primary operation (Fig 3)

In the present ten year follow up of 157 patients with pleomorphic adenoma primarily diagnosed by fine needle aspiration biopsy and thereafter surgically treated, there were only three recurrences In two of the three patients the primary extirpation was not total In no case was the recurrent growth sub cutaneous or cutaneous

Spontaneous extension of prostatic carcinoma through the fascia of Denonvillier and involvement of the rectal mucosa seems to be uncommon YOUNG (1945) found 12 cases and McCREA & KARAFIN (1958) 6 cases of rectal tumour invasion in 800 and 500 patients, respectively In the present series of 469 patients with cytologically verified prostatic carcinoma four had invasion of the rectum before needle biopsy was performed In necropsy series the frequency of rectal involvement has been reported as 8 to 11 per cent (DOSSOT 1930 ELKIN & MUELLER 1954 FRANKS 1956)

In only one of the 469 patients in the present series did rectal invasion appear after aspiration biopsy There was no indication that the spread had occurred via the needle track The interval of three years between aspiration biopsy and manifest rectal involvement was too great to suggest any causal relationship to the biopsy

Hormonal medication was the only treatment given for the prostatic carcinoma in these 469 patients One may speculate whether or not the hormonal therapy which was instituted immediately after the diagnosis was established by aspiration biopsy could have prevented tumour growth along the needle track through the rectal wall However 73 of the 469 patients had poorly differentiated carcinoma and 70 per cent of these 73 patients were dead within three years of diagnosis which indicated a poor response to hormonal therapy It seems very unlikely therefore that this therapy had any effect in preventing tumour growth along the needle track in these patients

The negative results of the present clinical investigation concerning evidence of local tumour extension produced by fine needle biopsy can be contrasted with the experimental demonstration in rabbits that malignant cells escaped through the capsular perforations caused by needling of metastatic lymph nodes The most probable explanation of the negative clinical findings is that the numbers

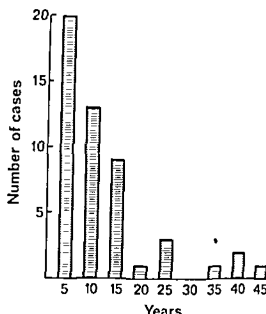


Fig 3 Time lapse from the treatment of *original tumour to the diagnosis of local* recurrence in 50 patients with recurrent pleomorphic adenoma of the parotid gland

noma cells, such cells were found also outside the capsule of the node at the sites of puncture This suggests that tumour cells may escape through the capsular perforations caused by fine needle biopsy of an encapsulated tumour, and may spread along the needle track ZAJICEK (1970) observed that blood escaping through the needle track after aspiration biopsy of mammary carcinoma could contain tumour cells

The clinical significance of these observations is difficult to evaluate, as most malignant tumours, the area of needling included, are subjected to subsequent therapeutic measures such as surgical excision or radiotherapy In a previous five year follow up of 656 patients with cervical lymph node metastases diagnosed by aspiration biopsy, there was no clinical evidence of local tumour growth resulting from the biopsy (ENGZELL et coll 1971)

The clinical part of the present investigation comprised follow up of patients with pleomorphic adenoma of the major salivary glands or carcinoma of the prostate All the tumours had been diagnosed by aspiration biopsy In these tumour types it seems reasonable to assume that spread of neoplastic cells resulting in tumour growth along the needle track would be revealed during clinical follow up

The incidence of postoperative recurrence of pleomorphic adenomas of the *major salivary glands has been reported as varying from* 0 *to almost* 50 per cent (AHLBOM 1935, MCFARLAND 1942, BUXTON et coll 1953 EDVALL 1954 FRA

ZELL 1954 BEAHRS et coll 1960 GRAGE et coll 1961) It has been stated that a high postoperative recurrence rate must be ascribed to insufficient removal of salivary gland tissue leaving small tumour excrescences (BEAHRS et coll 1960 GRAGE et coll 1961, ENEROTH 1964)

In our experience most recurrences appear within ten years of the removal of the original tumour Of 50 recurrent pleomorphic adenomas treated at Karolinska Sjukhuset between 1955 and 1965 33 (66 per cent) appeared within ten years of the primary operation (Fig 3)

In the present ten year follow up of 157 patients with pleomorphic adenoma primarily diagnosed by fine needle aspiration biopsy and thereafter surgically treated, there were only three recurrences In two of the three patients the primary extirpation was not total In no case was the recurrent growth subcutaneous or cutaneous

Spontaneous extension of prostatic carcinoma through the fascia of Denonvillier and involvement of the rectal mucosa seems to be uncommon YOUNG (1945) found 12 cases and McCREA & KARAFIN (1958) 6 cases of rectal tumour invasion in 800 and 500 patients respectively In the present series of 469 patients with cytologically verified prostatic carcinoma four had invasion of the rectum before needle biopsy was performed In necropsy series the frequency of rectal involvement has been reported as 8 to 11 per cent (DOSSOT 1930 ELKIN & MUELLER 1954 FRANKS 1956)

In only one of the 469 patients in the present series did rectal invasion appear after aspiration biopsy There was no indication that the spread had occurred via the needle track The interval of three years between aspiration biopsy and manifest rectal involvement was too great to suggest any causal relationship to the biopsy

Hormonal medication was the only treatment given for the prostatic carcinoma in these 469 patients One may speculate whether or not the hormonal therapy which was instituted immediately after the diagnosis was established by aspiration biopsy could have prevented tumour growth along the needle track through the rectal wall However 73 of the 469 patients had poorly differentiated carcinoma and 70 per cent of these 73 patients were dead within three years of diagnosis which indicated a poor response to hormonal therapy It seems very unlikely therefore that this therapy had any effect in preventing tumour growth along the needle track in these patients

The negative results of the present clinical investigation concerning evidence of local tumour extension produced by fine needle biopsy can be contrasted with the experimental demonstration in rabbits that malignant cells escaped through the capsular perforations caused by needling of metastatic lymph nodes The most probable explanation of the negative clinical findings is that the numbers

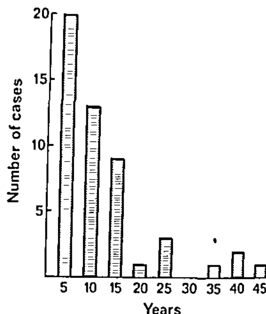


Fig 3 Time lapse from the treatment of original tumour to the diagnosis of local recurrence in 50 patients with recurrent pleomorphic adenoma of the parotid gland

noma cells, such cells were found also outside the capsule of the node at the sites of puncture This suggests that tumour cells may escape through the capsular perforations caused by fine needle biopsy of an encapsulated tumour, and may spread along the needle track ZAJICEK (1970) observed that blood escaping through the needle track after aspiration biopsy of mammary carcinoma could contain tumour cells

The clinical significance of these observations is difficult to evaluate, as most malignant tumours, the area of needling included, are subjected to subsequent therapeutic measures such as surgical excision or radiotherapy In a previous five year follow up of 656 patients with cervical lymph node metastases diagnosed by aspiration biopsy, there was no clinical evidence of local tumour growth resulting from the biopsy (ENGZELL et coll 1971)

The clinical part of the present investigation comprised follow up of patients with pleomorphic adenoma of the major salivary glands or carcinoma of the prostate All the tumours had been diagnosed by aspiration biopsy In these tumour types it seems reasonable to assume that spread of neoplastic cells resulting in tumour growth along the needle track would be revealed during clinical follow up

The incidence of postoperative recurrence of pleomorphic adenomas of the major salivary glands has been reported as varying from 0 to almost 50 per cent (AHLBOM 1935 MCFARLAND 1942, BUXTON et coll 1953 EDVALL 1954 FRA

ZELL 1954, BEAHRS et coll 1960, GRAGE et coll 1961) It has been stated that a high postoperative recurrence rate must be ascribed to insufficient removal of salivary gland tissue leaving small tumour excrescences (BEAHRS et coll 1960 GRAGE et coll 1961, ENEROTH 1964)

In our experience most recurrences appear within ten years of the removal of the original tumour Of 50 recurrent pleomorphic adenomas treated at Karolinska Sjukhuset between 1955 and 1965 33 (66 per cent) appeared within ten years of the primary operation (Fig 3)

In the present ten year follow up of 157 patients with pleomorphic adenoma primarily diagnosed by fine needle aspiration biopsy and thereafter surgically treated there were only three recurrences In two of the three patients the primary extirpation was not total In no case was the recurrent growth subcutaneous or cutaneous

Spontaneous extension of prostatic carcinoma through the fascia of Denonvilliers and involvement of the rectal mucosa seems to be uncommon YOUNG (1945) found 12 cases and MCCREA & KARAFIN (1958) 6 cases of rectal tumour invasion in 800 and 500 patients respectively In the present series of 469 patients with cytologically verified prostatic carcinoma four had invasion of the rectum before needle biopsy was performed In necropsy series the frequency of rectal involvement has been reported as 8 to 11 per cent (DOSSOT 1930 ELKIN & MUELLER 1954 FRANKS 1956)

In only one of the 469 patients in the present series did rectal invasion appear after aspiration biopsy There was no indication that the spread had occurred via the needle track The interval of three years between aspiration biopsy and manifest rectal involvement was too great to suggest any causal relationship to the biopsy

Hormonal medication was the only treatment given for the prostatic carcinoma in these 469 patients One may speculate whether or not the hormonal therapy which was instituted immediately after the diagnosis was established by aspiration biopsy could have prevented tumour growth along the needle track through the rectal wall However 73 of the 469 patients had poorly differentiated carcinoma and 70 per cent of these 73 patients were dead within three years of diagnosis which indicated a poor response to hormonal therapy It seems very unlikely therefore that this therapy had any effect in preventing tumour growth along the needle track in these patients

The negative results of the present clinical investigation concerning evidence of local tumour extension produced by fine needle biopsy can be contrasted with the experimental demonstration in rabbits that malignant cells escaped through the capsular perforations caused by needling of metastatic lymph nodes The most probable explanation of the negative clinical findings is that the numbers

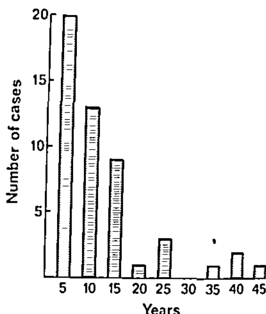


Fig 3 Time lapse from the treatment of original tumour to the diagnosis of local recurrence in 50 patients with recurrent pleomorphic adenoma of the parotid gland

noma cells, such cells were found also outside the capsule of the node at the sites of puncture *This suggests that tumour cells may escape through the capsular perforations caused by fine needle biopsy of an encapsulated tumour, and may spread along the needle track* ZAJICEK (1970) observed that blood escaping through the needle track after aspiration biopsy of mammary carcinoma could contain tumour cells

The clinical significance of these observations is difficult to evaluate, as most malignant tumours, the area of needling included, are subjected to subsequent therapeutic measures such as surgical excision or radiotherapy In a previous five year follow up of 656 patients with cervical lymph node metastases diagnosed by aspiration biopsy, there was no clinical evidence of local tumour growth resulting from the biopsy (ENGZELL et coll 1971)

The clinical part of the present investigation comprised follow up of patients with pleomorphic adenoma of the major salivary glands or carcinoma of the prostate All the tumours had been diagnosed by aspiration biopsy In these tumour types it seems reasonable to assume that spread of neoplastic cells resulting in tumour growth along the needle track would be revealed during clinical *follow up*

The incidence of postoperative recurrence of pleomorphic adenomas of the major salivary glands has been reported as varying from 0 to almost 50 per cent (AHLBOM 1935, McFARLAND 1942 BUXTON et coll 1953, EDVALL 1954, FRA

The prognosis of mammary carcinoma diagnosed by aspiration biopsy was investigated by ROBBINS et coll (1954) and BERG & ROBBINS (1962) at the Memorial Hospital New York where the method was introduced for the diagnosis of malignancy in the early 1930s. On the basis of a comparative five year follow up ROBBINS et coll concluded that aspiration biopsy had no effect on survival rates in mammary carcinoma BERG & ROBBINS later compared the 15 year actuarial survival rate among 370 patients operated upon for mammary carcinoma following aspiration biopsy with the corresponding rate in 370 closely matched controls in whom the diagnosis had been made by other means The survival rates in the two case series were identical The writers concluded that clinically no reason can be found not to use aspiration biopsy when it is indicated

SUMMARY

The possibility of spread of tumour cells in connection with aspiration biopsy of lymph node metastases was investigated in experiments on rabbits with popliteal metastases from Vx2 carcinoma By cannulating lymph and blood were sampled and analyzed Following digital massage of the node before needle biopsy tumour cells were found in one of seven experiments in lymph and in one of nine experiments in blood Subsequent fine needle (18-gauge) biopsy did not seem to cause further vascular dissemination of carcinoma cells Fluid material escaping through the capsular perforations of the node caused by the needle contained tumour cells in ten of twelve experiments Clinical follow up was made of 157 patients with pleomorphic adenoma of the major salivary glands and of 469 patients with prostatic carcinoma all diagnosed by fine needle (22 gauge) biopsy No evidence emerged of recurrent or locally extended growth attributable to the biopsy

ZUSAMMENFASSUNG

Die Möglichkeit der Tumorzellverschleppung bei Aspirationsbiopsie von Lymphknotenmetastasen wurde experimentell an Kaninchen mit poplitealen Metastasen eines Vx2 Karzinoms geprüft Durch Kanülierung wurde Lymphe und Blut gewonnen und auf Tumorzellen untersucht Vor der Nadelbiopsie wurde eine digitale Massage des Lymphknotens durchgeführt Tumorzellen wurden hiernach in der Lymphe in einem von sieben und im Blut in einem von neun Versuchen gefunden Die nachfolgende Feinnadelbiopsie (Nadel Nr 18) schien nicht zu einer weiteren vaskulären Ausschwemmung von Tumorzellen zu führen Die Gewebsflüssigkeit die aus den durch die Nadel verursachten Perforationen der Lymphkapsel austrat enthielt in zehn von zwölf Versuchen Tumorzellen Hundertsiebenundfünfzig Patienten mit einem pleomorphen Adenom der grossen Speicheldrüsen und 469 Patienten mit einem Prostatakarzinom deren Diagnose in allen Fällen mittels Feinnadelpunktion (Nadel Nr 22) gestellt wurde wurden klinisch nachuntersucht Ein Zusammenhang zwischen Biopsie und rezidivierendem oder lokal sich ausdehnendem Tumorwachstum liess sich nicht feststellen

of cells which entered the needle tracks were relatively small, and that these cells were destroyed before they could give rise to local tumour growth Similar conclusions were formed by other writers from investigations on the fate of implanted tumour cells (GRACE & KONDO 1958, MOORE et coll 1959, WEISS 1967, WILLIS 1967, FOULDS 1969)

The literature contains numerous reports on the spread of tumour cells via blood vessels in connection with manipulation of tumours, including surgery (ENGEL 1955, ROBERTS et coll 1958, ENGEL 1959, GRIFFITHS & SALSBURY 1965, GOLDBLATT & NADEL 1965, FOULDS 1969) But we have found no reports on investigation on the possible spread of tumour cells through efferent lymphatics or blood vessels in connection with fine needle aspiration biopsy

In order to investigate this question, we cannulated efferent lymphatics and veins in rabbits with popliteal lymph node metastases from Vx2 carcinoma Efferent lymph and blood were sampled and analyzed for tumour cells After gentle massage of the metastasis bearing node, carcinoma cells could be demonstrated in the lymph in one of seven experiments and in the blood in one of nine experiments (cf FJERNBERG & ZAJICEK 1965) There was no evidence that fine needle (18 gauge) biopsy released Vx2 carcinoma cells or cell clusters into the lymphatic or the blood circulation However, since individual Vx2 carcinoma cells cannot always be confidently distinguished on a morphologic basis from large lymphoid cells (ENGZELL et coll 1968), the possibility that some carcinoma cells were transported by the lymph or blood draining from the needled metastasis could not be excluded The general opinion however is that individual circulating tumour cells may perish without giving rise to metastatic growth, and it has been shown that the presence of tumour cells in the circulating blood bears no relation to the prognosis of the disease (ENGEL 1955, 1959, MOORE et coll 1959, MALMGREN 1967, FOULDS 1969)

Our investigations thus indicated that, although it is likely that tumour cells spread along the needle tracks of aspiration biopsy, this possible spread lacks practical clinical implications Distant dissemination of tumour cells through lymphatics or blood vessels following fine needle biopsy seems to be uncommon to judge from our experiments on rabbits The use of fine needle aspiration biopsy in the diagnosis of malignancy therefore should not involve a risk of impaired prognosis

The lack of effect on prognosis has been demonstrated in carcinoma of the kidney and the breast VON SCHREEB et coll (1967) analyzed the five year survival rate in 77 patients who were operated upon for renal carcinoma following puncture and injection of contrast medium into the tumour A comparison with 73 matched controls in whom puncture was not made revealed no significant difference in survival rates

ENGZELL U JAKOBSSON P A SIGURDSON A and ZAJICEK J Aspiration biopsy of m tastatic carcinoma in lymph nodes of the neck A review of 1101 consecutive cases To be published in Acta oto laryng (1971)

— RUBIO C TJERNBERG B and ZAJICEK J The lymph node barrier against Vx2 cancer cells before durin and after lymphography Europ J Cancer 4 (1968) 305

ESPOSTI P L Cytologic malignancy grading of prostatic carcinoma by transrectal aspiration biopsy A five year follow up study of 469 hormone treated patients Scand J Urol Nephrol 5 (1971) 199

FOULDS L Neoplastic development Academic Press London and New York 1969

FRANKS L M The spread of prostatic cancer J Path Bact 72 (1956) 603

FRANZEN S GIERTZ G and ZAJICEK J Cytological diagnosis of prostatic tumours by trans rectal aspiration biopsy Brit J Urol 32 (1960) 193

FRAZELL E L Clinical aspects of tumors of the major salivary glands Cancer 7 (1954) 637

GOLDBLATT S A and NADEL E L Cancer cells in the circulating blood a critical review II Acta cytol 9 (1965) 6

GOLDMAN E J and SAMELLAS W Local extention of carcinoma of the prostate following needle biopsy J Urol 84 (1960) 575

GRACE JR J T and KONDO T Investigation of host resistance in cancer patients Ann Surg 148 (1958) 633

GRAGE T B LOBER P H and SHAHON D B Benign tumors of the major salivary glands Surgery 50 (1961) 625

GRIFFITHS J D and SALSBURY A J Circulatin cancer cells Charles C. Thomas Springfield Illinois 1965

LABARDINI M M and NESBIT R M Perineal extension of adenocarcinoma of the prostate gland after punch biopsy J Urol 97 (1967) 891

MALMGREN R A Studies of circulating cancer cells in cancer patients *In* Mechanisms of in asion in cancer p 108 Edited by P Denoix Springer Verlag Berlin 1967

MARTIN H E and ELLIS E B Biopsy by needle puncture and aspiration Ann Surg 92 (1930) 169

— — Aspiration biopsy Surg Gynec Obstet 59 (1934) 578

— and STEWART F W The advantages and limitations of aspiration biopsy Amer J Roent genol 35 (1936) 245

MCCREA L E and KARAFIN L Carcinoma of the prostate Metastases therapy and survival A statist cal analysis of five hundred cases J intern Coll Surg 29 (1958) 723

MCFARLAND J The histopathologic prognosis of salivary gland mixed tumours Amer J med Sci 203 (1942) 502

MOORE G E SANDBERG A A and WATNE A L Factors involved in the spread of malignant cells Roswell Park Mem Inst Bull 4 (1959) 49

ROBBINS G F BROTHERS J H EBERHART W F and QUAN S Is aspiration biopsy of breast cancer dangerous to the patient? Cancer 7 (1954) 774

ROBERTS S WATNE A McGRATH R McGREW E and COLE W H Techniques and results of isolation of cancer cells from the circulating blood Arch Surg 76 (1958) 334

ROFE P The cells of normal urine J clin Path 8 (1955) 25

VON SCHREEB T ARNER O SKOVSTED G and WIKSTAD N Renal adenocarcinoma Is there a risk of spreading tumour cells in diagnostic puncture? Scand J Urol Nephrol 1 (1967) 270

SODERSTROM N Fine needle aspiration b opsy Almqvist & Wiks ll Stockholm 1966

TJERNBERG B Lymphography An animal study on the diagnosis of Vx2 carcinoma and in flammation Acta radiol (1962) Suppl No 214

RÉSUMÉ

Les auteurs ont étudié la possibilité de dissémination de cellules tumorales par l'aspiration biopsie de ganglions lymphatiques métastatiques par une expérimentation sur les lapins atteints de métastases poplitées de carcinome Vx2. Ils ont analysé de la lymphe et du sang recueillis par cathétérisme des vaisseaux. Après massage digital du ganglion avant la biopsie à l'aiguille, on a trouvé des cellules tumorales dans la lymphe dans un cas sur sept et dans le sang dans un cas sur neuf. Une biopsie ultérieure faite avec une aiguille fine (calibre 18) ne paraît pas avoir causé d'autres disséminations vasculaires de cellules cancéreuses. Le liquide qui sortait à travers les trous d'aiguille de la capsule ganglionaire contenait des cellules tumorales dans dix cas sur douze. Les auteurs ont suivi l'évolution clinique de 157 malades atteints d'adénomes pléomorphiques des glandes salivaires principales et de 469 malades atteints de cancer de la prostate, tous diagnostiqués par biopsie avec une aiguille fine (calibre 22). Il n'y a pas eu de signe de récidive ou de dissémination locale attribuable à la biopsie.

REFERENCES

ACKERMAN, L. V. and WHEAT, M. W.: The implantation of cancer — an avoidable surgical risk? Surgery 37 (1955), 341.

AHLBOM, H. E.: Mucous- and salivary gland tumours. Acta radiol. (1935) Suppl. No. 23.

BANGLE, JR., R.: Appraisal of needle biopsy. Postgrad. Med. 29 (1961), 138.

BEAHRS, O. H., WOOLNER, L. B., CARVETH, S. W. and DEVINE, K. D.: Surgical management of parotid lesions. Arch. Surg. 80 (1960), 890.

BERG, J. W. and ROBBINS, G. F.: A late look at the safety of aspiration biopsy. Cancer 15 (1962), 826.

BURKHOLDER, G. V. and KAUFMAN, J. J.: Local implantation of carcinoma of the prostate with percutaneous needle biopsy. J. Urol. 95 (1966), 801.

BUXTON, R. W., MAXWELL, J. H. and FRENCH, A. J.: Surgical treatment of epithelial tumors of the parotid gland. Surg. Gynec. Obstet. 97 (1953), 401.

CACHIN, Y., GUERRIER, Y. et PINEL, J.: Les adénopathies cervicales néoplasiques. Librarie Arnette, Paris 1969.

CLARKE, B. G., LEADBETTER, W. F. and CAMPBELL, J. S.: Implantation of cancer of the prostate in site of perineal needle biopsy: report of a case. J. Urol. 70 (1953), 937.

CRILE, G. and HAZARD, J. B.: Classification of thyroiditis, with special reference to the use of needle biopsy. J. clin. Endocrin. 11 (1951), 1123.

DOSSOT, R.: Cancer of the prostate. Its origin and extension. J. Urol. 23 (1930), 217.

EDVALL, C. A.: Mucous- and salivary gland tumours: a presentation of 330 cases treated radiosurgically. Acta chir. scand. 107 (1954), 313.

ELKIN, M. and MUELLER, H. P.: Metastases from cancer of the prostate. Cancer 7 (1954), 1246.

ENEROTH, C. M.: Histological and clinical aspects of parotid tumours. Acta oto-laryng. (1964) Suppl. No. 191.

ENGEL, H. C.: Cancer cells in the circulating blood: a clinical study on the occurence of cancer cells in the peripheral blood and in venous blood draining the tumour area at operation. Acta chir. scand. (1955) Suppl. No. 201.

— Cancer cells in the blood. A five to nine year follow up study. Ann. Surg. 149 (1959), 457.

ENGZELL U JAKOBSSON P A SIGURDSON A and ZAJICEK J Aspiration biopsy of metastatic carcinoma in lymph nodes of the neck A review of 1101 consecutive cases To be published in Acta oto laryng (1971)

— RUBIO C TJERNBERG B and ZAJICEK J The lymph node barrier against Vx2 cancer cells before during and after lymphography Europ J Cancer 4 (1968) 305

ESPOSTI P L Cytologic malignancy grading of prostatic carcinoma by transrectal aspiration biopsy A five year follow up study of 469 hormone treated patients Scand J Urol Nephrol 5 (1971) 199

FOULDS L Neoplastic development Academic Press London and New York 1969

FRANKS L M The spread of prostatic cancer J Path Bact 72 (1956) 603

FRANZEN S GIERTZ G and ZAJICEK J Cytological diagnosis of prostatic tumours by transrectal aspiration biopsy Brit J Urol 32 (1960) 193

FRAZELL E L Clinical aspects of tumors of the major salivary glands Cancer 7 (1954) 637

GOLDBLATT S A and NADEL E L Cancer cells in the circulating blood a critical review II Acta cytol 9 (1965) 6

GOLDMAN E J and SAMELLAS W Local extention of carcinoma of the prostate following needle biopsy J Urol 84 (1960) 575

GRACE JR J T and KONDO T Investigation of host resistance in cancer patients Ann Surg 148 (1958) 633

GRAGE T B LOBER P H and SHAHON D B Benign tumors of the major salivary glands Surgery 50 (1961) 625

GRIFFITHS J D and SALSBURY A J Circulating cancer cells Charles C. Thomas Springfield Illinois 1965

LABARDINI M M and NESBIT R M Perineal extension of adenocarcinoma of the prostate gland after punch biopsy J Urol 97 (1967) 891

MALMGREN R A Studies of circulating cancer cells in cancer patients *In* Mechanisms of invasion in cancer p 108 Edited by P Denoix Springer Verlag Berlin 1967

MARTIN H E and ELLIS E B Biopsy by needle puncture and aspiration Ann Surg 92 (1930) 169

— — Aspiration biopsy Surg Gynec Obstet 59 (1934) 578

— and STEWART F W The advantages and limitations of aspiration biopsy Amer J Roentgenol 35 (1936) 245

McCREA L E and KARAFIN L Carcinoma of the prostate Metastases therapy and survival A statistical analysis of five hundred cases J intern Coll Surg 29 (1958) 723

McFARLAND J The histopathologic prognosis of salivary gland mixed tumours Amer J med Sci 203 (1942) 502

MOORE G E SANDBERG A A and WATNE A L Factors involved in the spread of malignant cells Roswell Park Mem Inst Bull 4 (1959) 49

ROBBINS G F BROTHERS J H EBERHART W F and QUAN S *Is aspiration* biopsy of breast cancer dangerous to the patient? Cancer 7 (1954) 774

ROBERTS S WATNE A McGRATH R McGREW E and COLE W H Techniques and results of isolation of cancer cells from the circulating blood Arch Surg 76 (1958) 334

ROFE P The cells of normal urine J clin Path 8 (1955) 25

VON SCHREEB T ARNER O SKOVSTED G and WIKSTAD N Renal adenocarcinoma Is there a risk of spreading tumour cells in diagnostic puncture? Scand J Urol Nephrol 1 (1967) 270

SODERSTROM N Fine needle aspiration biopsy Almqvist & Wiksell Stockholm 1966

TJERNBERG B Lymphography An animal study on the diagnosis of Vx2 carcinoma and inflammation Acta radiol (1962) Suppl No 214

— and ZAJICEK J Cannulation of lymphatics leaving cancerous nodes in studies on tumor spread Acta cytol 9 (1965) 197

WEISS L The cell periphery metastasis and other contact phenomena North Holland Publishing Co Amsterdam 1967

WILLIS R A The pathology of tumours Fourth edition Butterworths London 1967

YOUNG H H The cure of cancer of the prostate by radical perineal prostatectomy (prostato seminal vesiculectomy) history literature and statistics of Young s operation J Urol 53 (1945), 188

ZAJICEK J Unpublished results 1970

FROM THE DEPARTMENT OF GYNECOLOGY (DIRECTOR PER KOLSTAD) OF THE NORWEGIAN RADIUM HOSPITAL AND NORSK HYDRO'S INSTITUTE FOR CANCER RESEARCH (DIRECTOR REIDAR EKER), OSLO, NORWAY

RADIOACTIVE COLLOIDAL GOLD IN THE TREATMENT OF OVARIAN CARCINOMA

by

J. CHR. AURE, K. HØEG and P. KOLSTAD

The intraperitoneal application of radioactive gold in the treatment of ovarian carcinoma has been widely used since MULLER in 1949 introduced the method. While the palliative effect of radioactive gold in cases of ascites due to carcinomatosis has been confirmed by a great number of investigators (KEETTEL et coll. 1966, KOTTMEIER 1968, MOORE & LANGLEY 1967, MULLER 1950, RUBIN 1962, VILLASANTA & BLOEDORN 1953), opinions regarding the curative effect have been contradictory. MULLER (1968) considered that the life saving contribution of radiogold was established. Other authors have also reported higher survival rates with this therapy in cases with no spread beyond the ovaries (MOORE & LANGLEY 1967). The curative effect is, however, denied by some (ANDREWS & ROOT 1953, KOTTMEIER 1968, RANDALL 1955, VILLASANTA & BLOEDORN 1968).

KEETTEL et coll. (1966) in peritoneal cytologic investigations noted that certain stage I ovarian carcinomas with intact capsules shed abnormal cells; this might result in late recurrence and death in otherwise favourable lesions. They therefore recommended the use of radioactive gold to counteract and destroy such cells, and reported a significant increase in the survival rate by this measure.

Submitted for publication 31 August 1970.

Table 1

Radiotherapy in cases of carcinoma in relation to stage

Therapy	Stage I	Stage II	Stage III	Stage IV	Total
No radiotherapy	15 (6.9 %)	2 (1.3 %)	10 (5.9 %)	13 (14.1 %)	40
Roentgen 250 kV	55 (25.1 %)	42 (27.5 %)	20 (11.7 %)	10 (10.9 %)	127
Betatron 31 MeV	98 (44.7 %)	80 (52.3 %)	84 (49.1 %)	49 (53.3 %)	311
Betatron 31 MeV and radioactive gold	51 (23.3 %)	29 (18.9 %)	57 (33.3 %)	20 (21.7 %)	157
Total	219 (100 %)	153 (100 %)	171 (100 %)	92 (100 %)	635

Accidental rupture of a tumor during the operation represents a particular problem for it is generally believed that in the case of rupture of a cystic carcinoma this has a markedly unfavourable effect on the prognosis (PUROLA & NIEMINEN 1968), some authors however doubt this assumption (GROGAN 1967, MALLOY et coll. 1965, MUNNELL & TAYLOR 1949).

We have employed radioactive colloidal gold in the treatment of ovarian carcinoma since 1954, the results of which in 77 cases were reviewed in 1964 by ØKLAND. At that time only 21 cases had been followed up for more than five years and as the results were not correlated with the tumor type or clinical stage no definite conclusions were possible.

Material and Methods. Problems concerning tumor type and prognosis arising in a series of 990 cases of ovarian carcinoma treated in the period 1945—1964 were discussed in two previous papers (AURE et coll. 1970). As mentioned above, radioactive gold began to be used in 1954 so that the significance of this type of treatment has been determined by reviewing all cases treated from 1955 to 1964. The number of primary epithelial tumors of the ovary in these years totalled 743, 635 of which were true carcinomas and 108 neoplasms of low potential malignancy. Histologic classification and clinical staging were performed by the FIGO method (SANTESSON & KOTTMEIER 1968). All cases were treated surgically and in addition the majority received some form of irradiation therapy. Forty cases of proved carcinoma had had no irradiation therapy during the primary treatment period but had been operated upon elsewhere and were admitted with recurrences. This group was therefore a selected one and has been excluded from the discussion. Cases with tumors of low potential malignancy were also on principle treated both surgically and radiologically. However, 14 patients received no irradiation therapy, most of them because they were relatively young (Table 2).

Table 2

Radiotherapy in relation to stage in cases of tumors of low potential malignancy

ıerapy	St ge I	Stage II	Stage III	Total
o rad otherapy	12 (13 8)	0 —	2 (40 0)	14
oentgen 250 kV	16 (18 4)	6 (37 5)	0 —	22
etat on 31 MeV	36 (41 4)	9 (56 2)	0 —	45
etatron 31 MeV and ıd oact e gold	23 (26 4)	1 (6 3)	3 (60 0)	27
Total	87 (100)	16 (100)	5 (100)	108

Table 3

Five year survival rates in cases of carcinoma in relation to sta e operability and therapy

Cl nical stag	Roentgen 250 kV		Betatron 31 MeV		Betatron 31 MeV and radioactive gold	
	No of cases	Alive	No of ca es	Ali e	No of cases	Alive
Stage I	55	28 (50 9)	98	62 (63 3)	51	43 (84 3)
Stage II tumor completely removed	17	7 (41 2)	23	7 (30 4)	15	8 (53 3)
Stag II tumor not ompletely remo ed	25	7 (28 0)	57	11 (19 3)	14	1 (7 1)
Stag III tumor ompletely r mo ed	0	0 —	9	2 (22 2)	15	6 (37 5)
Stag III tumor not completely r mo ed	20	1 (5 0)	75	5 (6 7)	42	4 (9 5)
St ge IV	10	1 (10 0)	49	4 (8 2)	20	1 (5 0)

Radiotherapy was in the earlier years of the period given by conventional 250 kV roentgen machines with two anterior and two posterior pelvic portals and 3 000 R to each field 149 cases in all received this type of treatment A 31 MeV betatron machine was installed in 1957 and a total of 356 cases of the present eries were treated through a 20 cm circular pelvic field with two opposing portals in a calculated midpelvic do e of up to between 4 000 and 5 000 rad Combined betatron therapy and intraperitoneal application of radioactive colloidal gold were administered to 157 cases with true invasive carcinomas and 27 cases of low potential malignancy The external irradiation dose in the e cases

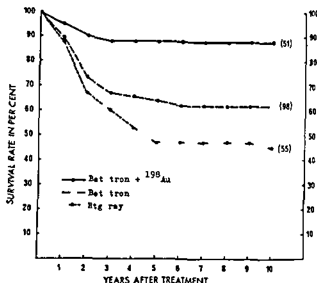


Fig 1 Comparison of survival rates according to the life table technique for stage I carcinomas in relation to radiotherapy Number of cases in parentheses

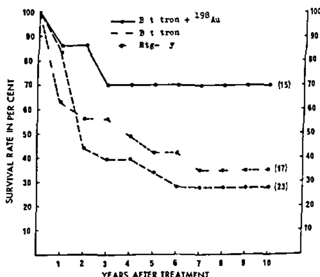


Fig 2 Comparison of survival rates according to the life table technique for stage II carcinomas with no tumor left at operation in relation to radiotherapy Number of cases in parentheses

was reduced to approximately 3 000 rad, the amount of radioactive gold varying between 75 mCi and 175 mCi, although usually 100 mCi Application was always made during laparotomy so that the whole peritoneal cavity could be inspected and palpated to ensure that no extensive adhesions were present The choice of radiotherapy was not made at random

All cases have been controlled for at least 5 years, and survival curves constructed using the life table technique The 5 year survival rates have been compared by means of the chi square test and within groups comprising relatively few cases, by means of the Yate correction

Table 4

Comparison of 5-year survival rates according to the life table technique for cases of stage I carcinoma with and without accidental rupture of tumor

Therapy	Rupture of tumor				No rupture of tumor			
	No of cases	Dead	Too short observation	Survival rate	No of cases	Dead	Too short observation	Survival rate
Roentgen 250 kV	6	4	0	33 3	49	25	1	48 6
Betatron 31 MeV	25	11	0	55 9	73	24	3	66 7
Betatron 31 MeV and radioactive gold	21	3	1	85 0	30	4	1	86 3
Total	52	18	1	64 8	152	53	5	64 6

Results

A comparison of the 5 year survival rates in cases of invasive carcinoma in relation to stage and operability is presented in Table 3 Cumulative survival curves for stage I carcinomas appear in Fig 1 and for stage II carcinomas with no tumor left at operation in Fig 2 Because of the superficial irradiation delivered by radioactive gold it was assumed that only in cases with microimplantations of carcinoma could an improvement of prognosis be achieved Stages II and III were therefore subdivided into groups based on whether all macroscopic malignant tissue had been removed or not Table 3 indicates that the 5 year survival rates were higher in the cases treated with radioactive gold than in those that had received betatron or conventional roentgen irradiation provided that no macroscopic malignant tissue had been left behind For stage I cases the difference in the 5 year survival rate between the betatron series and the radioactive gold series was statistically significant ($p < 0\ 01$) The 5 year survival rates for stage II and stage III tumor completely removed also presented the same tendency as for stage I However the differences observed in the rates were not statistically significant The 5 year survival rates seemed to be independent of the type of irradiation used in cases in which complete removal of all macroscopic malignant tissue was impossible

Accidental rupture of the tumor occurred in 55 cases (25 %) in the series of 219 stage I cases with invasive carcinoma Rupture of the tumor occurred with equal frequency in all tumor types The 5 year survival rate was 64 8 % and the 10 year survival rate 51 3 % in cases with rupture of the tumor The cor

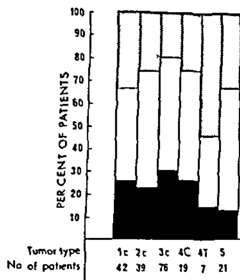


Fig 3 Survey of type of radiotherapy used for stage I carcinomas in relation to tumor type 1c — serous carcinoma 2c — mucinous carcinoma 3c — endometrioid carcinoma 4C — mesonephroid carcinoma clear cell type 4T — mesonephroid carcinoma with tubular pattern 5 — undifferentiated carcinoma ◻ roentgen 250 kV ◻ betatron 31 MeV ■ betatron 31 MeV and radioactive gold

responding figures for cases without rupture of tumor were 64 6 and 50 9 %. Thus, rupture of tumor did not appear to worsen the prognosis The 5 year survival rates in relation to therapy are given for cases with and without rupture of the tumor in Table 4, the survival rates were the same in all the different treatment groups

It has been repeatedly demonstrated that great variations in prognosis exist according to tumor type (KOTTMEIER 1968, SANTESSON & KOTTMEIER 1968) The selection of radiotherapy was not performed at random in the present series and the review disclosed that radioactive gold was given less frequently in undifferentiated carcinoma and mesonephroid carcinoma than in the other tumor types (Fig 3) The improved prognosis for the radioactive gold series might therefore be explained by the greater frequency of the more benign types The results of treatment for stage I carcinomas in relation to tumor type are given in Table 5 It appears that the 5 year survival rates for the different tumor types depend upon the choice of radiotherapy The lowest survival was attained in the 250 kV roentgen irradiation group and the highest in the radioactive gold group The chi square test in each tumor group indicated that the differences were not statistically significant However, it should be pointed out that the survival rate for cases treated with radioactive gold was without exception higher, irrespective of the histologic type

Cumulative 5 year survival rates for stage I cases of tumors of low potential malignancy appear in Table 6 As the prognosis for these cases is generally excellent, no conclusions can be drawn It should be pointed out, however, that the lowest survival rate occurred in those receiving no radiotherapy

Table 5

Five year survival rates for stage I carcinomas in relation to tumor type and type of radiotherapy

Tumor type	Roentgen 250 kV		Betatron 31 MeV		Betatron 31 MeV and radioactive gold	
	No of cases	Alive	No of cases	Alive	No of cases	Alive
Serous	14	7 (50.0 %)	17	11 (64.7 %)	11	9 (81.8 %)
Mucinous	10	7 (70.0 %)	20	14 (70.0 %)	9	8 (88.9 %)
Endometrioid	15	8 (53.3 %)	38	28 (73.7 %)	23	20 (87.0 %)
Mesonephroid	9	5 (55.6 %)	11	7 (63.6 %)	6	5 (83.3 %)
Undifferentiated	7	1 (14.3 %)	12	4 (33.3 %)	2	1 (50.0 %)
Total	5	28 (50.8 %)	98	64 (65.3 %)	51	43 (84.3 %)

Table 6

Cumulative 5-year survival rates according to the life table technique in relation to therapy in cases of stage I tumors of low potential malignancy

Therapy	No of cases	Dead	Too short observation	Survival rate
No radiotherapy	17	2	1	83
Roentgen 250 kV	16	0	1	100.0
Betatron 31 MeV	36	1	5	97.0 %
Betatron 31 MeV and radioactive gold	23	0	7	100.0

Conclusions

The present investigation was retrospective. Irradiation therapy during the period was not standardized and the choice of radiotherapy was not at random. Conclusions should therefore be drawn with great care. No difference in survival rates was observed between groups in which the tumor was not completely removed. A striking feature however was the significantly better results for stage I cases treated with radioactive gold than for those receiving conventional roentgen irradiation or betatron only. When the stage I cases were divided into groups based on the histologic type of tumor, the number within each group was too small for valid comparisons. Each group however exhibited the same tendency as the whole series, survival rates being 14 to 20 % higher for cases treated with

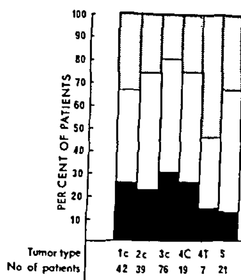


Fig 3 Survey of type of radiotherapy used for stage I carcinomas in relation to tumor type 1c — serous carcinoma 2c — mucinous carcinoma 3c — *endometrioid carcinoma* 4C — mesonephroid carcinoma clear cell type 4T — mesonephroid carcinoma with tubular pattern 5 — undifferentiated carcinoma ☐ roentgen 250 kV ☐ betatron 31 MeV ■ betatron 31 MeV and radioactive gold

responding figures for cases without rupture of tumor were 64 6 and 50 9 % Thus, rupture of tumor did not appear to worsen the prognosis The 5 year survival rates in relation to therapy are given for cases with and without rupture of the tumor in Table 4, the survival rates were the same in all the different treatment groups

It has been repeatedly demonstrated that great variations in prognosis exist according to tumor type (KOTTMEIER 1968, SANTESSON & KOTTMEIER 1968) *The selection of radiotherapy was not performed at random in the present series* and the review disclosed that radioactive gold was given less frequently in undifferentiated carcinoma and mesonephroid carcinoma than in the other tumor types (Fig 3) The improved prognosis for the radioactive gold series might therefore be explained by the greater frequency of the more benign types The results of treatment for stage I carcinomas in relation to tumor type are given in Table 5 It appears that the 5 year survival rates for the different tumor types depend upon the choice of radiotherapy The lowest survival was attained in the 250 kV roentgen irradiation group and the highest in the radioactive gold group The chi square test in each tumor group indicated that the differences were not statistically significant However, it should be pointed out that the survival rate for cases treated with radioactive gold was without exception higher, irrespective of the histologic type

Cumulative 5 year survival rates for stage I cases of tumors of low potential malignancy appear in Table 6 As the prognosis for these cases is generally excellent, no conclusions can be drawn It should be pointed out, however, that the lowest survival rate occurred in those receiving no radiotherapy

Table 5

Five year survival rates for stage I carcinomas in relation to tumor type and type of radiotherapy

Tumor type	Roentgen 250 kV		Betatron 31 MeV		Betatron 31 MeV and radioactive gold	
	No of cases	Alive	No of cases	Alive	No of cases	Alive
Serous	14	7 (50.0 %)	17	11 (64.7 %)	11	9 (81.8 %)
Mucinous	10	7 (70.0 %)	20	14 (70.0 %)	9	8 (88.9 %)
Endometrioid	15	8 (53.3 %)	38	28 (73.7 %)	23	20 (87.0 %)
Mesonephroid	9	5 (55.6 %)	11	7 (63.6 %)	6	5 (83.3 %)
Undifferentiated	7	1 (14.3 %)	12	4 (33.3 %)	2	1 (50.0 %)
Total	55	28 (50.8 %)	98	64 (65.3 %)	51	43 (84.3 %)

Table 6

Cumulative 5-year survival rates according to the life table technique in relation to therapy in cases of stage I tumors of low potential malignancy

Therapy	No of cases	Dead	Too short observation	Survival rate
No radiotherapy	12	2	1	83.3
Roentgen 250 kV	16	0	1	100.0
Betatron 31 MeV	36	1	5	97.0
Betatron 31 MeV and radioactive gold	23	0	7	100.0

Conclusions

The present investigation was retrospective. Irradiation therapy during the period was not standardized and the choice of radiotherapy was not at random. Conclusions should therefore be drawn with great care. No difference in survival rates was observed between groups in which the tumor was not completely removed. A striking feature however was the significantly better results for stage I cases treated with radioactive gold than for those receiving conventional roentgen irradiation or betatron only. When the stage I cases were divided into groups based on the histologic type of tumor, the number within each group was too small for valid comparisons. Each group however exhibited the same tendency as the whole series, survival rates being 14 to 20 % higher for cases treated with

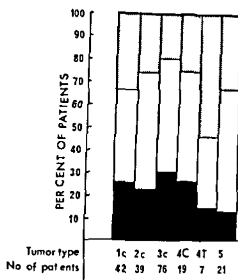


Fig 3 Survey of type of radiotherapy used for stage I carcinomas in relation to tumor type 1c — serous carcinoma 2c — mucinous carcinoma 3c — endometrioid carcinoma 4C — mesonephroid carcinoma clear cell type 4T — mesonephroid carcinoma with tubular pattern 5 — undifferentiated carcinoma ☐ roentgen 250 kV ☐ betatron 31 MeV ■ betatron 31 MeV and radioactive gold

responding figures for cases without rupture of tumor were 64 6 and 50 9 % Thus, rupture of tumor did not appear to worsen the prognosis The 5 year survival rates in relation to therapy are given for cases with and without rupture of the tumor in Table 4, the survival rates were the same in all the different treatment groups

It has been repeatedly demonstrated that great variations in prognosis exist according to tumor type (KOTTMEIER 1968, SANTESSON & KOTTMEIER 1968) The selection of radiotherapy was not performed at random in the present series and the review disclosed that radioactive gold was given less frequently in undifferentiated carcinoma and mesonephroid carcinoma than in the other tumor types (Fig 3) The improved prognosis for the radioactive gold series might therefore be explained by the greater frequency of the more benign types The results of treatment for stage I carcinomas in relation to tumor type are given in Table 5 It appears that the 5 year survival rates for the different tumor types depend upon the choice of radiotherapy The lowest survival was attained in the 250 kV roentgen irradiation group and the highest in the radioactive gold group The chi square test in each tumor group indicated that the differences were not statistically significant However, it should be pointed out that the survival rate for cases treated with radioactive gold was without exception higher, irrespective of the histologic type

Cumulative 5 year survival rates for stage I cases of tumors of low potential malignancy appear in Table 6 As the prognosis for these cases is generally excellent, no conclusions can be drawn It should be pointed out, however, that the lowest survival rate occurred in those receiving no radiotherapy

REFERENCES

ANDREWS G A ROOT S W KNISELY R M and KERMAN H H Intracavitary use of colloidal radioactive gold Radiology 61 (1953) 922

AURE J CHR HOEG K and KOLSTAD P Clinical and histological studies of ovarian carcinoma Long term follow up of 990 cases Obstet and Gynec 37 (1971) 1

— — — Psammoma bodies in serous carcinoma of the ovary A prognostic study Amer J Obstet Gynec 109 (1971) 113

DAHLE T og BLOM HARTVIGSEN F Radioaktivt gull (Au[198]) i behandlingen av cancer (In Norw eg an) T norske Lægeforen 75 (1955) 41

ELAHI E H LONG M E FRICK H C and SOMMERS S C Long term survival in disseminated ovarian carcinoma Amer J Obstet Gynec 99 (1967) 522

GROGAN R H Accidental rupture of malignant ovarian cysts during surgical removal Obstet and Gynec 30 (1967) 716

KEETTEL W C FOX M R LONGNECKER D S and LATOURETTE H B Prophylactic use of radioactive gold in the treatment of primary ovarian cancer Amer J Obstet Gynec 94 (1966) 766

KOTTMEIER H L Proposals for the standardization of the combined treatment of ovarian cancer *In* Ovarian cancer p 257 UICC Monograph Series Vol 11 Springer Verlag Berlin 1968

LONG R T L JOHNSON R E and SALA J M Variations in survival among patients with carcinoma of the ovary Analysis of 253 cases according to histologic type anatomical stage and method of treatment Cancer 20 (1967) 1195

MALLOY J J DOCKERTY M B WELSH J S and HUNT A B Papillary ovarian tumors Amer J Obstet Gynec 93 (1965) 867

MOORE D W and LANGLEY I I Routine use of radiogold following operation for ovarian cancer Amer J Obstet Gynec 98 (1967) 624

MORTON D G Ovarian carcinoma Amer J Obstet Gynec 95 (1966) 359

MUNNELL E W and TAYLOR H C Ovarian carcinoma Amer J Obstet Gynec 58 (1949) 943

MÜLLER J H Weitere Entwicklung der Therapie von Peritonealcarzinosen bei Ovarialcarzinom mit kunstlicher Radioaktivitat Gynaecologia (Basel) 129 (1950) 289

— Intraperitoneal colloidal radiogold [1] Au therapy in ovarian cancer *In* Ovarian Cancer p 198 UICC Monograph Series Vol 11 Springer Verlag Berlin 1968

OKLAND G Radioaktivt gull ved cancer ovarii (In Norwegian) Nord Med 71 (1964) 719

PUROLA E and NIEMINEN O Does rupture of cystic carcinoma during operation influence the prognosis? Ann Chir Gynaec Fenn 57 (1968) 615

RANDALL J H Treatment of ovarian carcinoma Evaluation of results at State University of Iowa Hospitals Obstet and Gynec 5 (1955) 445

RUBIN P A critical analysis of current therapy of carcinoma of the ovary Amer J Roentgenol 88 (1962) 833

SANTESSON L and KOTTMEIER H L General classification of ovarian tumors *In* Ovarian Cancer p 1 UICC Monograph Series Vol 11 Springer Verlag Berlin 1968

VILLASANTA V and BLOEDORN F G Operation external irradiation radioactive isotopes and chemotherapy in treatment of metastatic ovarian malignancy Amer J Obstet Gynec 102 (1968) 531

radioactive gold than for those given external irradiation only. A similar trend was evident for stage II and stage III cases with no macroscopic remnants of the neoplasm left at operation. There consequently appears to be justification for suggesting that treatment with radioactive gold combined with external irradiation will probably produce better results in such; this is in agreement with other reports (KEETTEL et coll. 1966, MOORE & LANGLEY 1967, MULLER 1968).

Against a widespread belief it would appear that rupture of the tumor at operation does not seem to influence the prognosis. The same conclusion was reached by GROGAN (1967), MALLOY et coll. (1965), and MUNNELL & TAYLOR (1949).

The present investigation affords no conclusions as regards the value of irradiation therapy in tumors of low potential malignancy.

As already stressed it seems that the advantages of radioactive gold have not been proved. Definite conclusions can only be reached by controlled clinical trials in which both the stage and tumor type are taken into consideration. During the last three years the treatment of all stage I and II ovarian carcinomas has been randomised, half the cases receiving radioactive gold, and the other half external high voltage irradiation only. Similar trials have been set up for stage III cases, *external irradiation alone or combined with chemotherapy being the* alternatives. Certain conclusions about the best therapy for ovarian carcinoma cannot be drawn until a sufficiently large series of cases have been controlled for a relatively long period.

SUMMARY

A retrospective investigation of 743 cases of primary epithelial carcinoma of the ovary of which 184 were treated by the postoperative intraperitoneal application of radioactive gold is presented. This treatment may effectively destroy microscopic metastases in the peritoneal cavity.

ZUSAMMENFASSUNG

Es wird über eine retrospektive Untersuchung von 743 Fällen, von denen 184 postoperativ mit radioaktivem Gold wegen eines primären Epithelkarzinoms des Ovariums behandelt wurden, berichtet. Diese Behandlungsmethode kann mikroskopische Metastasen in der Bauchhöhle zerstören.

RÉSUMÉ

Les auteurs présentent une étude rétrospective de 743 cas d'épithélioma primitif de l'ovaire dont 184 traités par injection intrapéritonéale post-opératoire d'or radioactif. Ce traitement peut effectivement détruire des métastases microscopiques dans la cavité péritonéal.

REFERENCES

ANDREWS G A ROOT S W KNISELY R M and KERMAN H H Intracavitary use of colloidal radioactive gold Radiology 61 (1953) 92?

AURE J CHR HOEG K and KOLSTAD P Clinical and histological studies of ovarian carcinoma Long term follow up of 990 cases Obstet and Gynec 37 (1971) 1

— — — Psammoma bodies in serous carcinoma of the ovary A prognostic study Amer J Obstet Gynec 109 (1971) 113

DAHLE T OF BLOM HARTVIGSEN F Radioaktivt gull (Au[198]) i behandlingen av cancer (In Norwegian) T norske Lægeforen 75 (1955) 41

ELAHI E H LONG M E FRICK H C and SOMMERS S C Long term survival in disseminated ovarian carcinoma Amer J Obstet Gynec 99 (1967) 522

GROGAN R H Accidental rupture of malignant ovarian cysts during surgical removal Obstet and Gynec 30 (1967) 716

KEETTEL W C FOX M R LONGNECKER D S and LATOURETTE H B Profylactic use of radioactive gold in the treatment of primary ovarian cancer Amer J Obstet Gynec 94 (1966) 766

KOTTMEIER H L Proposals for the standardization of the combined treatment of ovarian cancer *In* Ovarian cancer p 257 UICC Monograph Series Vol 11 Springer Verlag Berlin 1968

LONG R T L JOHNSON R F and SALA J M Variations in survival among patients with carcinoma of the ovary Analysis of 253 cases according to histologic type anatomical stage and method of treatment Cancer 20 (1967) 1195

MALLOY J J DOCKERTY M B WELCH J S and HUNT A B Papillary ovarian tumors Amer J Obstet Gynec 93 (1965) 867

MOORE D W and LANGLEY I I Routine use of radiogold following operation for ovarian cancer Amer J Obstet Gynec 98 (1967) 624

MORTON D G Ovarian carcinoma Amer J Obstet Gynec 95 (1966) 359

MUNNELL E W and TAYLOR H C Ovarian carcinoma Amer J Obstet Gynec 58 (1949) 943

MÜLLER J H Weitere Entwicklung der Therapie von Peritonealcarzinosen bei Ovarialcarzinom mit künstlicher Radioaktivität Gynaecologia (Basel) 129 (1950) 289

— Intraperitoneal colloidal radiogold [198]Au therapy in ovarian cancer *In* Ovarian Cancer p 198 UICC Monograph Series Vol 11 Springer Verlag Berlin 1968

OKLAND G Radioaktivt gull ved cancer ovarii (In Norwegian) Nord Med 71 (1964) 719

PUROLA E and NIEMINEN O Does rupture of cystic carcinoma during operation influence the prognosis Ann Chir Gynaec Fenn 57 (1968) 615

RANDALL J H Treatment of ovarian carcinoma Evaluation of results at State University of Iowa Hospitals Obstet and Gynec 5 (1955) 445

RUBIN P A critical analysis of current therapy of carcinoma of the ovary Amer J Roentgenol 88 (196?) 833

SANTESSON L and KOTTMEIER H L General classification of ovarian tumors *In* Ovarian Cancer p 1 UICC Monograph Series Vol 11 Springer Verlag Berlin 1968

VILLASANTA V and BLOEDORN F G Operation external irradiation radioactive isotopes and chemotherapy in treatment of metastatic ovarian malignancy Amer J Obstet Gynec 102 (1968) 531

radioactive gold than for those given external irradiation only A similar trend was evident for stage II and stage III cases with no macroscopic remnants of the neoplasm left at operation There consequently appears to be justification for suggesting that treatment with radioactive gold combined with external irradiation will probably *produce better results in such, this is in agreement with other* reports (KEETTEL et coll 1966, MOORE & LANGLEY 1967, MULLER 1968)

Against a widespread belief it would appear that rupture of the tumor at operation does not seem to influence the prognosis The same conclusion was reached by GROGAN (1967), MALLOY et coll (1965), and MUNNELL & TAYLOR (1949)

The *present investigation affords no conclusions as regards the value of* irradiation therapy in tumors of low potential malignancy

As already stressed it seems that the advantages of radioactive gold have not been proved Definite conclusions can only be reached by controlled clinical trials in which both the stage and tumor type are taken into consideration *During the last three years the treatment of all stage I and II ovarian carcinomas* has been randomised, half the cases receiving radioactive gold, and the other half external high voltage irradiation only Similar trials have been set up for stage III cases, external irradiation alone or combined with chemotherapy being the alternatives Certain conclusions about the best therapy for ovarian carcinoma *cannot be drawn until a sufficiently large series of cases have been controlled for* a relatively long period

SUMMARY

A retrospective investigation of 743 cases of primary epithelial carcinoma of the ovary of which 184 were treated by the postoperative intraperitoneal application of radioactive gold is presented This treatment may effectively destroy microscopic metastases in the *peritoneal cavity*

ZUSAMMENFASSUNG

Es wird uber eine retrospektive Untersuchung von 743 Fallen von denen 184 postoperativ mit radioaktivem Gold wegen eines primaren Epithelkarzinoms des Ovariums behandelt wurden berichtet Diese Behandlungsmethode kann mikroskopische Metastasen in der Bauchhohle zerstoren

RÉSUMÉ

Les auteurs presentent une etude retrospective de 743 cas d epithelioma primitif de l ovaire dont 184 traites par injection intraperitoneale post operatoire d or radioactif Ce traitement peut effectivement detruire des metastases microscopiques dans la cavite peritoneal

REFERENCES

ANDREWS G A ROOT S W KNISELY R M and KERMAN H H Intracavitary use of colloidal radioactive gold Radiology 61 (1953) 922

AURE J CHR HOEG K and KOLSTAD P Clinical and histological studies of ovarian carcinoma Long term follow up of 990 cases Obstet and Gynec 37 (1971) 1

— — — Psammoma bodies in serous carcinoma of the ovary A prognostic study Amer J Obstet Gynec 109 (1971) 113

DAHLE T og BLOM HARTVIGSEN F Radioaktivt gull (Au[198]) i behandlingen av cancer (In Norwegian) T norske Lægeforen 75 (1955) 41

ELAHI E H LONG M E FRICK H C and SOMMERS S C Long term survival in disseminated ovarian carcinoma Amer J Obstet Gynec 99 (1967) 522

GROGAN R H Accidental rupture of malignant ovarian cysts during surgical removal Obstet. and Gynec 30 (1967) 716

KEETTEL W C FOX M R LONGNECKER D S and LATOURETTE H B Prophylactic use of radioactive gold in the treatment of primary ovarian cancer Amer J Obstet Gynec 94 (1966) 766

KOTTMEIER H L Proposals for the standardization of the combined treatment of ovarian cancer *In* Ovarian cancer p 257 UICC Monograph Series Vol 11 Springer Verlag Berlin 1968

LONG R T L JOHNSON R E and SALA J M Variations in survival among patients with carcinoma of the ovary Analysis of 953 cases according to histologic type anatomical stage and method of treatment Cancer 20 (1967) 1195

MALLOY J J DOCKERTY M B WELCH J S and HUNT A B Papillary ovarian tumors Amer J Obstet Gynec 93 (1965) 867

MOORE D W and LANGLEY I I Routine use of radiogold following operation for ovarian cancer Amer J Obstet Gynec 98 (1967) 624

MORTON D G Ovarian carcinoma Amer J Obstet Gynec 95 (1966) 359

MUNNELL E W and TAYLOR H C Ovarian carcinoma Amer J Obstet Gynec 58 (1949) 943

MÜLLER J H Weitere Entwicklung der Therapie von Peritonealcarzinosen bei Ovarialcarzinom mit künstlicher Radioaktivität Gynaecologia (Basel) 129 (1950) 289

— Intraperitoneal colloidal radiogold [198]Au therapy in ovarian cancer *In* Ovarian Cancer p 198 UICC Monograph Series Vol 11 Springer Verlag Berlin 1968

OKLAND G Radioaktivt gull ved cancer ovarii (In Norwegian) Nord Med 71 (1964) 719

PUROLA E and NIEMINEN O Does rupture of cystic carcinoma during operation influence the prognosis? Ann Chir Gynaec Fenn 57 (1968) 615

RANDALL J H Treatment of ovarian carcinoma Evaluation of results at State University of Iowa Hospitals Obstet and Gynec 5 (1955) 445

RUBIN P A critical analysis of current therapy of carcinoma of the ovary Amer J Roentgenol 88 (1962) 833

SANTESSON L and KOTTMEIER H L General classification of ovarian tumors *In* Ovarian Cancer p 1 UICC Monograph Series Vol 11 Springer Verlag Berlin 1968

VILLASANTA V and BLOEDORN F G Operation external irradiation radioactive isotopes and chemotherapy in treatment of metastatic ovarian malignancy Amer J Obstet Gynec 102 (1968) 531

FROM THE DEPARTMENTS OF RADIOLOGY AND NEUROSURGERY AND THE SECOND DIVISION OF SURGERY, FACULTY OF MEDICINE, KYOTO UNIVERSITY, JAPAN

INTRA-OPERATIVE IRRADIATION IN ABDOMINAL AND CEREBRAL TUMOURS

by

M. ABE, M. FUKUDA, K. YAMANO, S. MATSUDA and H. HANDA

Radiotherapy is rarely employed for abdominal neoplasms in adults since these are mostly radioresistant adenocarcinomas and external irradiation to the abdomen inevitably causes intestinal damage. Surgery has therefore been preferred either for curative or palliative purposes for practically all abdominal tumours. Recent developments in anesthesia and antibiotics have also assisted in this choice although the elimination of cancer nests around major blood vessels is still well nigh impossible. Microscopic lesions may remain even if the operation is considered radical. The problems obviously cannot be resolved by surgery alone.

Intra-operative irradiation has therefore been developed. The resectable lesions are treated by surgery and the remaining malignant remnants sterilized by irradiation with a single massive dose during the operation (2, 3, 9, 12). This method has two advantages. First, an adequate field may be determined with accuracy under direct vision, otherwise impossible to achieve. Secondly, since normal organs adjacent to the tumour may be moved from the field so that the lesion to be irradiated may be exposed directly to radiation any damage to the

Submitted for publication 16 July 1970



Fig 1 Intra-operative irradiation to carcinoma of the stomach with an electron beam

normal structures is minimized These advantages made it possible to deliver a sufficient dose to the abdominal neoplasm without affecting the small intestine

This type of radiotherapy demands however that the largest possible dose administered at one session to the tumour area must be smaller than the tolerance dose of normal critical organs that cannot be moved from the field Any possible success with radiotherapy depends of course upon a safe ratio or differential between the dose delivered to the new growth and that to the normal tissue The cancerocidal dose is generally agreed to be about 6 000 R in the case of fractionated irradiation but there is little information available for determining the equivalent single dose for intra operative irradiation (4 7, 13) From data published on intra-operative irradiation (5 6 8 10 11) and the authors fundamental experiment (1) it was estimated that 2 500 to 4 000 R may be a single dose equivalent to 6 000 R given fractionately This new radiotherapy has been applied mostly in cases where surgery cannot remove the primary growth in the abdomen its local spread and regional lymph node metastases

Method The irradiation is planned and executed by a team of radiologists and surgeons The operation is performed most conveniently in an irradiation room With no betatron and the intra operative irradiation carried out with ^{60}Co the patient is moved under general anesthesia from an operation theatre to the ^{60}Co room A betatron was, however, eventually installed in a theatre in which the operation could also be performed Irradiation in carcinoma of the stomach usually took place following the gastrectomy and before the suturing because at this stage the site to be irradiated can be adequately exposed and the organs to be protected pulled aside Careful control of the general anesthesia is necessary during the irradiation to prevent movement, the condition of the patient being observed by a distant monitoring system Fig 1 depicts intra operative irradiation with an electron beam in a patient with carcinoma of the stomach

FROM THE DEPARTMENTS OF RADIOLOGY AND NEUROSURGERY AND THE SECOND DIVISION OF SURGERY, FACULTY OF MEDICINE, KYOTO UNIVERSITY, JAPAN

INTRA-OPERATIVE IRRADIATION IN ABDOMINAL AND CEREBRAL TUMOURS

by

M. Abe, M. Fukuda, K. Yamano, S. Matsuda and H. Handa

Radiotherapy is rarely employed for abdominal neoplasms in adults since these are mostly radioresistant adenocarcinomas and external irradiation to the abdomen inevitably causes intestinal damage. Surgery has therefore been preferred either for curative or palliative purposes for practically all abdominal tumours. Recent developments in anesthesia and antibiotics have also assisted in this choice although the elimination of cancer nests around major blood vessels is still well nigh impossible. Microscopic lesions may remain even if the operation is considered radical. The problems obviously cannot be resolved by surgery alone.

Intra-operative irradiation has therefore been developed. The resectable lesions are treated by surgery and the remaining malignant remnants sterilized by irradiation with a single massive dose during the operation (2, 3, 9, 12). This method has two advantages. First, an adequate field may be determined with accuracy under direct vision, otherwise impossible to achieve. Secondly, since normal organs adjacent to the tumour may be moved from the field so that the lesion to be irradiated may be exposed directly to radiation any damage to the

Submitted for publication 16 July 1970

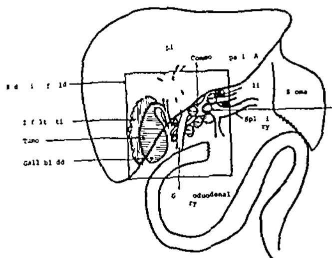


Fig 2 Field localization in a patient with carcinoma of the gallbladder

Carcinoma of the stomach Twenty nine patients with carcinoma of the stomach were treated with intra operative irradiation The patients were divided into three groups

Group 1 Patients (five) in an advanced stage who received only exploratory laparotomy or shunt operation Intra operative irradiation was administered to patients in this group to alleviate symptoms and prolong life Doses ranging from 1 800 to 3 000 R from a ^{60}Co source were delivered to the tumour during laparotomy in 4 patients and 4 000 R with 20 MeV electrons in one patient The effect of a single dose of 1 800 R was not apparent, but remission of stenosis from large masses was obtained about two weeks after exposure in 4 patients who received more than 2 000 R

Illustrative case Female aged 30 with inoperable carcinoma of the stomach was ad mitted complaining of difficulty in swallowing any kind of solid or semi solid food Laparotomy revealed carcinoma of the cardia infiltrating the entire stomach The proximal gastric segment was irradiated with a single dose of 3 000 R and gastrostomy was performed for tube feeding There was marked improvement in the stenosis beginning as early as the second week after the exposure and continuing until the patient died with general metastases on the 114th day following irradiation

Group 2 Patients (sixteen) with malignant remnants as a result of incomplete excision of neoplasms This group is the most suitable for intra-operative irradia tion An attempt was made to sterilize with radiation the lesions that usually remain in the infrahepatic region including the porta hepatis the celiac trunk

Case reports and Results

Carcinoma of the pancreas Two cases were treated but only one could be followed

Illustrative case Female aged 75 with carcinoma of the head of the pancreas was the first to be treated with intra operative irradiation When admitted she was jaundiced and had a large firm mass in the upper abdomen Laparotomy revealed that it was about 5 cm in size and lay in the head of the pancreas with lymph node metastases extending into the duodenum the gallbladder was distended The tumour was considered inoperable After choledocho jejunostomy a single dose of 2 500 R was delivered from a ^{60}Co source to the surface of the main mass through a 5 8 cm×3 6 cm field The stomach and small intestine were retracted from the field with stay sutures and the region tightly packed with towels Jaundice disappeared within a few weeks while the abdominal mass regressed and was not palpable at the time of discharge 30 days after the irradiation The patient had no symptoms for about 200 days until she again developed nausea and vomiting Further laparotomy 31 weeks after the first irradiation disclosed that the mass was reduced to about a third of the size reco ded at the first irradiation Preceding gastro jejunostomy a second intra operative irradiation this time with 2 000 R was applied to the main mass including the infiltrated duodenum through a 4 cm×4 cm field Although the post operative course was smooth the patient died suddenly of cerebral hemorrhage seven days after the second irradiation Histologic examination of the irradiated main tumour disclosed an adenocarcinoma with a few cells in a dense fibrous stroma Concern had been felt about perforation of or bleeding from the exposed duodenum but a marked regeneration of the intestinal villi occurred and no complications were evident throughout the survival period Autopsy revealed small metastases in the liver lungs skeleton and kidneys

Carcinoma of the biliary system Three patients were treated Marked regression was evident at autopsy in 2 of these and at exploratory laparotomy in the other

Illustrative case Female aged 58 with a large mass about 8 cm in diameter in the right infra hepatic region and invading the adjacent liver with numerous lymph node metastases around the common hepatic artery at laparotomy The growth was diagnosed as carcinoma of the gallbladder and considered inoperable A single dose of 2 500 R 18 MeV electron radiation was given through a 10 cm×10 cm field (Fig 2) A T tube was inserted through the common bile duct in order to prevent obstructive jaundice a procedure followed by partial gastrectomy The patient tolerated the procedure well and recovered satisfactorily A large amount of muddy discharge consisting of tissue debris was drained via the tube at the tenth post irradiation day and at the same time a significant elevation of the serum transaminase was recorded Three weeks later the mass in the right upper abdomen disappeared Two months after irradiation a rise in temperature suggesting a peritoneal abscess led to a second laparotomy This revealed marked regression of the mass The primary tumour and the hepatic metastases had become a cyst about 5 cm in size with a smooth surface and containing serous pus and encapsuled by firm scar tissue The cyst was evacuated and for the purpose of intra arterial infusion chemotherapy a teflon tube was inserted into the common hepatic artery A total of 4 500 mg 5FU was continuously infused via the catheter for three weeks The patient had no symptoms or signs four months after intra operative irradiation Histologic comparison of the biopsy specimens obtained at both operations indicated a definite carcinostatic effect from the irradiation

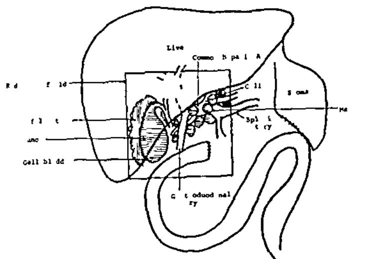


Fig 2 Field localization in a patient with carcinoma of the gallbladder

Carcinoma of the stomach Twenty nine patients with carcinoma of the stomach were treated with intra-operative irradiation The patients were divided into three groups

Group 1 Patients (five) in an advanced stage who received only exploratory laparotomy or shunt operation Intra operative irradiation was administered to patients in this group to alleviate symptoms and prolong life Doses ranging from 1 800 to 3 000 R from a ^{60}Co source were delivered to the tumour during laparotomy in 4 patients and 4 000 R with 20 MeV electrons in one patient The effect of a single dose of 1 800 R was not apparent but remission of stenosis from large masses was obtained about two weeks after exposure in 4 patients who received more than 2 000 R

Illustrative case Female aged 30 with inoperable carcinoma of the stomach was admitted complaining of difficulty in swallowing any kind of solid or semi solid food Laparotomy revealed carcinoma of the cardia infiltrating the entire stomach The proximal gastric segment was irradiated with a single dose of 3 000 R and gastrostomy was performed for tube feeding There was marked improvement in the stenosis beginning as early as the second week after the exposure and continuing until the patient died with general metastases on the 114th day following irradiation

Group 2 Patients (sixteen) with malignant remnants as a result of incomplete excision of neoplasms This group is the most suitable for intra operative irradiation An attempt was made to sterilize with radiation the lesions that usually remain in the infrahepatic region including the porta hepatis, the celiac trunk

Case reports and Results

Carcinoma of the pancreas Two cases were treated but only one could be followed

Illustrative case Female aged 75 with carcinoma of the head of the pancreas was the first to be treated with intra operative irradiation When admitted she was jaundiced and had a large firm mass in the upper abdomen Laparotomy revealed that it was about 5 cm in size and lay in the head of the pancreas with lymph node metastases extending into the duodenum the gallbladder was distended The tumour was considered inoperable After choledocho jejunostomy a single dose of 2 500 R was delivered from a ^{60}Co source to the surface of the main mass through a 5 8 cm×3 6 cm field The stomach and small intestine were retracted from the field with stay sutures and the region tightly packed with towels Jaundice disappeared within a few weeks while the abdominal mass regressed and was not palpable at the time of discharge 30 days after the irradiation The patient had no symptoms for about 200 days until she again developed nausea and vomiting Further laparotomy 31 weeks after the first irradiation disclosed that the mass was reduced to about a third of the size reco ded at the first irradiation Preceding gastro jejunostomy a second intra operative irradiation this time with 2 000 R was applied to the main mass including the infiltrated duodenum through a 4 cm×4 cm field Although the post operative course was smooth the patient died suddenly of cerebral hemorrhage seven days after the second irradiation Histologic examination of the irradiated main tumour disclosed an adenocarcinoma with a few cells in a dense fibrous stroma Concern had been felt about perforation of or bleeding from the exposed duodenum but a marked regeneration of the intestinal villi occurred and no complications were evident throughout the survival period Autopsy revealed small metastases in the liver lungs skeleton and kidneys

Carcinoma of the biliary system Three patients were treated Marked regression was evident at autopsy in 2 of these and at exploratory laparotomy in the other

Illustrative case Female aged 58 with a large mass about 8 cm in diameter in the right infra hepatic region and invading the adjacent liver with numerous lymph node metastases around the common hepatic artery at laparotomy The growth was diagnosed as carcinoma of the gallbladder and considered inoperable A single dose of 2 500 R 18 MeV electron radiation was given through a 10 cm×10 cm field (Fig 2) A T tube was inserted through the common bile duct in order to prevent obstructive jaundice a procedure followed by partial gastrectomy The patient tolerated the procedure well and recovered satisfactorily A large amount of muddy discharge consisting of tissue debris was drained via the tube at the tenth post irradiation day and at the same time a significant elevation of the serum trans aminase was recorded Three weeks later the mass in the right upper abdomen disappeared Two months after irradiation a rise in temperature suggesting a peritoneal abscess led to a second laparotomy This revealed marked regression of the mass The primary tumour and the hepatic metastases had become a cyst about 5 cm in size with a smooth surface and containing serous pus and encapsuled by firm scar tissue The cyst was evacuated and for the purpose of intra arterial infusion chemotherapy a teflon tube was inserted into the common hepatic artery A total of 4 500 mg 5FU was continuously infused via the catheter for three weeks The patient had no symptoms or signs four months after intra operative irradiation Histologic comparison of the biopsy specimens obtained at both operations indicated a definite carcinostatic effect from the irradiation

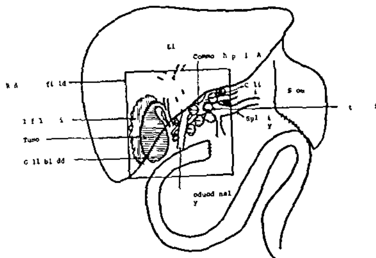


Fig 2 Field localization in a patient with carcinoma of the gallbladder

Carcinoma of the stomach Twenty nine patients with carcinoma of the stomach were treated with intra-operative irradiation The patients were divided into three groups

Group 1 Patients (five) in an advanced stage who received only exploratory laparotomy or shunt operation Intra operative irradiation was administered to patients in this group to alleviate symptoms and prolong life Doses ranging from 1 800 to 3 000 R from a ^{60}Co source were delivered to the tumour during laparotomy in 4 patients and 4 000 R with 20 MeV electrons in one patient The effect of a single dose of 1 800 R was not apparent but remission of stenosis from large masses was obtained about two weeks after exposure in 4 patients who received more than 2 000 R

Illustrative case Female aged 30 with inoperable carcinoma of the stomach was admitted complaining of difficulty in swallowing any kind of solid or semi solid food Laparotomy revealed carcinoma of the cardia infiltrating the entire stomach The proximal gastric segment was irradiated with a single dose of 3 000 R and gastrostomy was performed for tube feeding There was marked improvement in the stenosis beginning as early as the second week after the exposure and continuing until the patient died with general metastases on the 114th day following irradiation

Group 2 Patients (sixteen) with malignant remnants as a result of incomplete excision of neoplasms This group is the most suitable for intra operative irradiation An attempt was made to sterilize with radiation the lesions that usually remain in the infrahepatic region including the porta hepatis the celiac trunk

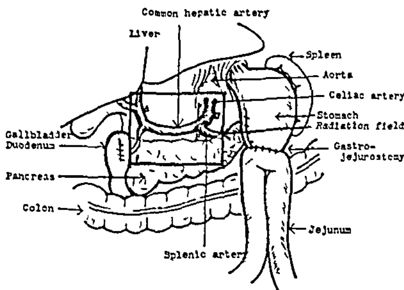


Fig. 3. Carcinoma of the stomach. The primary growth may be removed but metastases around vessels such as the celiac artery and portal vein may persist. Diagram of field localization used.

and its main branches as well as the para-aortic region. Fig. 3 depicts the radiation field. Five out of 16 patients survived more than a year and 2 patients are still alive, one after 27 months and one patient after 36 months, both have returned to work with no evidence of recurrence.

Group 3. Patients (eight) who underwent radical operation. An increase in the cure rate can be obtained only when microscopic lesions are eliminated. Intra-operative irradiation was administered to 8 patients who had had a radical operation. Three patients survived more than a year, one patient for two and half years, and one patient lived for three years without symptoms.

Carcinoma of the colon and retroperitoneal tumours. Intra-operative irradiation was given to 6 patients with carcinoma of the colon, and to one with recurrent carcinoma of the corpus uteri and with peritoneal reticulosarcoma. Two patients with growths of the caecum and one with a neoplasm of the sigmoid colon are alive, 2 of them with no sign of recurrence for three years.

Illustrative case. Male, aged 63, who had undergone right hemicolectomy for carcinoma of the colon five years previously, was admitted with abdominal distension and increasing pain in the back. Laparotomy revealed a recurrence near the terminal ileum which was about 5 cm in diameter and infiltrated the right iliac fossa and the nerve plexus. The main tumour was removed, but a large mass around the nerve plexus and the inferior vena cava was irradiated with 3 000 R ^{60}Co preceding colonic anastomosis. Histology revealed colloid carcinoma. Recovery was complete for about ten months until the patient again began to complain of epigastric pain and had a massive hematemesis. Further laparotomy revealed no obvious malignant lesion at the irradiated site. The patient died of hepatitis induced by surgery 307 days after irradiation.

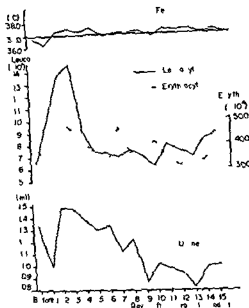


Fig 4 Changes in urine volume temperature and blood cell counts after intra operative irradiation in 29 patients with carcinoma of the stomach

Cerebral tumours Intra operative irradiation was administered to 2 patients with recurrent cerebral tumours who had once received a course of conventional post-operative radiotherapy

Illustrative cases Female aged 57 with an occipital tumour who had received 5 960 R from a ^{60}Co source after partial resection of a growth that was histologically a fibrosarcoma She was well for 8 months until she again developed hemiparesis and ataxia Further craniotomy disclosed a 5 cm recurrent tumour with invasion of the surrounding structures 3 cm below the dura The lesion was partly removed and a single dose of 3 500 R (8 MeV delivered through a 8 cm field The post-operative course was smooth and uneventful The patient was almost free from symptoms and signs for 5 months until she again developed ataxia and died 189 days after the irradiation

Female aged 37 with vertigo and anorexia A tumour in the right frontal region diagnosed as a glioblastoma was partly resected and 5 940 R from a ^{60}Co source given (fractionately Progression of the disease necessitated recraniotomy which disclosed an undemarcated mass in the frontotemporal region After partial resection a single dose of 4 000 R of 12 MeV electron energy was administered to the main lesion through a 4 cm field The post-operative course was uneventful until the patient became febrile 2 months later Probable radiation induced necrosis indicated craniotomy on the 63rd post irradiation day in which the irradiated region contained only necrotic tissues the temperature fell to normal after aspiration of the necrotic mass The patient again became febrile 2 weeks later and died on the 87th day following the irradiation Autopsy could not be performed

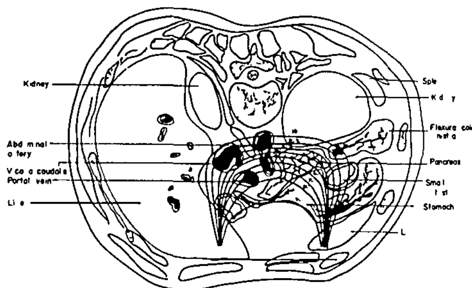


Fig 5 Percentage depth dose distribution of 18 MeV electron beam through an 8 cm field

Complications Almost all patients recovered without serious complications or deviations from the usual post operative course Wound healing, recovery of appetite and bowel function were not disturbed The urine, blood cell count and blood chemistry including S GOT, S GPT, alkaline and acid phosphatase bilirubin, blood urea nitrogen and protein fractions were frequently examined but no definite changes attributable to irradiation were apparent Fig 4 presents mean values of urine volume, fever, blood cell counts before and after intra operative irradiation in 29 patients with carcinoma of the stomach Exposure of the second part of the duodenum cannot be avoided in intra operative radiotherapy for carcinoma of the head of the pancreas Concern was therefore felt for possible perforation of or bleeding from this region, no such sequelae occurred however in the 2 000 to 2 500 R dose range The symptoms of 29 patients with carcinoma of the stomach were within tolerable limits following irradiation (Table)

Discussion

An electron beam with a sharp and rapid fall off in depth dose offers the particular advantage of minimizing the exposure of normal tissues located under tumours Fig 5 shows a depth dose distribution of irradiation with 18 MeV electrons An 80 per cent dose range down to the depth of the celiac artery leaves the bone marrow almost free from exposure A sterilising dose can there

Table

Symptoms (in per cent) of 29 patients with carcinoma of the stomach after intra-operative irradiation

	Before	Days after intra-operative irradiation														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Nausea	9.1	13.8	18.1	9.1	0	0	0	0	0	0	0	0	4.6	4.6	4.6	9.1
Vomiting	0	4.6	4.6	9.1	0	0	0	0	0	0	0	0	4.6	4.6	4.6	4.6
Vertigo	4.6	0	4.6	4.6	0	0	0	0	0	0	0	0	0	0	0	0
Anorexia	27.3	27.3	27.3	27.3	22.7	22.7	18.1	18.1	9.1	18.1	22.7	22.7	18.1	22.7	18.1	9.1
Insomnia	0	13.8	13.8	9.1	9.1	9.1	9.1	4.6	0	0	0	0	0	0	0	0
Fatigue	9.1	22.7	13.8	18.1	22.7	18.1	13.8	9.1	4.6	4.6	9.1	9.1	9.1	9.1	13.8	18.1
Pain	13.8	13.8	9.1	9.1	4.6	4.6	0	0	0	0	0	0	0	0	0	0
Diarrhea	0	0	0	0	4.6	0	0	0	0	0	0	0	0	0	0	0
Hematemesis	0	0	0	0	0	0	0	0	0	0	0	0	4.6	4.6	9.1	9.1
Melena	0	0	0	0	0	0	0	0	0	0	0	0	4.6	4.6	9.1	9.1

fore be delivered to the lesion with a sharp limitation of the total volume of tissue included in the high dose range. This characteristic may also be favourable for the treatment of cerebral tumours in which lesions are removed by operation and the remnants eliminated by direct exposure to an electron beam.

The number of patients treated by this method is insufficient and the follow-up period too short for a definite evaluation to be made. It is assumed that a single dose of at least 2 500 R is necessary as a cancerocidal dose for adenocarcinoma. Intra operative irradiation to abdominal tumours produces no harmful complications such as perforation of or bleeding from the intestine, diarrhea, anorexia or abdominal pain at a dosage less than 4 000 R measured at the surface of the tumour. Long term survival may be expected following intra-operative irradiation to localized small remnants or possible lesions that remain after operable lesions.

SUMMARY

A method of intra operative irradiation for the treatment of abdominal neoplasms is described. This consists in the irradiation of primary growths and malignant remnants during the course of ordinary radical surgery. The method appears to possess many advantages and the preliminary results seem most encouraging.

ZUSAMMENFASSUNG

Eine Methode für die intraoperative Bestrahlung von malignen Bauchtumoren nach operativer Freilegung wird beschrieben. Die Methode scheint mehrere Vorteile zu bieten und die vorläufigen Resultate erscheinen versprechend.

RÉSUMÉ

Description d une methode d irradiation per operatoire pour le traitement des tumeurs abdominales Elle consiste en l irradiation des tumeurs primitives et des parties malignes restantes au cours d une intervention chirurgicale radicale ordinaire Cette methode parait avoir de nombreux avantages et les resultats preliminaires semblent tres encourageants

REFERENCES

1 ABE M and ARAKAWA M *Fundamental studies on surgical irradiation Histological and* hematological changes followed by irradiation during laparotomy of dogs J Jap Cancer Th 2 (1967) 271

2 — YAMANO K and MATSUDA S *Intraoperative radiotherapy of abdominal tumors* Part III Intraoperative irradiation to carcinoma of the colon and retroperitoneal tumors Nipp Acta radiol 29 (1970) 1488

3 — — IMURA T and MATSUDA S Intraoperative radiotherapy of abdominal tumors Part I Intraoperative irradiation to carcinoma of the pancreas head and biliary *system Nipp Acta radiol 29 (1969) 75*

4 ANDREWS J R and MOODY J M The dose time relationship in radiotherapy Amer J Roentgenol 75 (1956) 590

5 BARTH G Erfahrungen und Ergebnisse mit der Nahbestrahlung operativ freigelegter Tumoren Strahlentherapie 91 (1953) 481

6 — und MEINEL I Intraoperative Kontakttherapie in den grossen Korperhohlen Strahlentherapie 109 (1959) 386

7 FOWLER J F and STERN B E Dose rate effects Some theoretical and practical consid *erations Brit J Radiol 33 (1960), 389*

8 FUCKS G und UEBERALL R Die intraoperative Rontgentherapie des Blasen Karzinoms Strahlentherapie 135 (1968) 280

9 FUKUDA M ABE M YAMANO K and MATSUDA S *Intraoperative radiotherapy of ab* dominal tumors Part II Intraoperative irradiation to carcinoma of the stomach Nipp Acta radiol 29 (1969) 390

10 GOIN L E and HOFFMAN E F The use of intravesical low voltage contact roentgen irra diation in cancer of the bladder Radiology 37 (1941) 545

11 LUTTERBECK E F Contact roentgen radiation of bladder tumors J Urol 82 (1959) 90

12 MATSUDA S SATOMURA K YAMANE M et coll Clinical study on surgical radiation therapy for advanced abdominal cancer J Jap Cancer Th 2 (1967) 279

13 STRANDQVIST M *Studien uber die kumulative Wirkung der Rontgenstrahlen bei Frak* tionierung Acta radiol (1944) Suppl No 55

FROM RADIUMHEMMET (DIRECTOR PROF J EINHORN) KAROLINSKA SJUKHUSET, STOCKHOLM SWEDEN

BILATERAL NEPHROBLASTOMA

A clinical review of 19 cases

by

BERTA JEREB

The prognosis in bilateral nephroblastoma remains poor although in the last two decades occasional reports of survivors have appeared (1—5 8—10 20 27, 28 31) The 19 bilateral cases now reviewed occurred among 334 cases of this condition reported in the Scandinavian countries between 1927 and 1967 — an incidence of 5 7 per cent Thirteen were treated in Sweden 2 in Norway and 4 case in Finland

Bilateral *nephroblastomas* present some interesting clinical features the prognosis is poorer than for the unilateral tumour and *the patients* are younger The diagnostic problems are reflected in the difficulty of choosing the appropriate therapy and *in the need for* numerous compromises Associated congenital anomalies are frequent

Material All the patients in whom nephroblastoma was detected in both kidneys during life have for the purpose of this review been considered as having bilateral nephroblastoma Eleven of the 19 patients (8 girls and 11 boys) were under one year of age one was 13 months three were 3 years three were 4 years

Submitted for publication 20 November 1970

Table 1

Two year cure rate for three methods of treatment of 15 patients of the present series (2 received no treatment and 2 were operated upon only)

	Bilateral irradiation				Unilateral irradiation			
	No chemotherapy		Chemotherapy		No chemotherapy		Chemotherapy	
	No	Cured	No	Cured	No	Cured	No	Cured
Nephrectomy + resection	—	—	3	2	5	0	2	1
Unilateral nephrectomy	1	0	3	0	—	—	—	—
Unilateral resection	—	—	1	1	—	—	—	—

and one 5 years old. The first sign of the disease in 7 children was haematuria and in the remaining 12 children was an abdominal swelling. Haematuria is more common in bilateral than in unilateral nephroblastoma (13). The abdominal swelling had been observed shortly after birth in 2 children but in one of these, four months elapsed before a diagnosis was made — when the swelling started to increase — and in the other a sudden change in the appearances of bilateral cystic kidneys at three years led to discovery of a tumour. Bilateral nephroblastoma was present in a 5 year old girl who had been under medical supervision for two years for bilateral malformation of the kidneys.

Bilateral disease was diagnosed before the first treatment in 13 patients, one of whom had pulmonary metastases on admission. The tumour in the second kidney was noticed later in 6 patients, in 4 of these within a year of the first treatment, in one after six and in the last after nine years. Metastases were detected, at the same time as the tumour, in the second kidney in 3 patients. Associated congenital malformations were present in 3 patients, bilateral kryptorchismus in 2 of these, one of whom also had hypospadias, while the third was a male intersex.

Two patients received no treatment at all and 2 only surgery, while in 15 patients surgery, radiotherapy and chemotherapy were combined (Table 1). Irradiation was applied to 26 tumour bed regions in 15 patients. In one patient given bilateral irradiation the dose is unknown and in one the dose was 1 000 rad to each side. One patient was treated on three occasions for recurrence, and over a period of 2 years received a dose of 4 300 rad to each region. The dose ranged from 1 500 to 3 000 rad in 12 patients and 18 regions. Radiotherapy

Table 2

Two year cure rate for the various methods of treatment of 19 patients

	No of cases	Cured
No treatment	2	—
Operation only	2*	—
Unilateral operation + bilateral irradiation	5	1
Bilateral operation + unilateral irradiation	7	1
Bilateral operation + bilateral irradiation	3	2

* One patient died at operation

Results

Patients free of symptoms for at least two years were regarded as cured since in an earlier series no metastases occurred more than fifteen months after the operation Of the 6 patients treated in the period 1943—59 none survived Of the 13 patients treated between 1960 and 1966 4 were alive and well at least two years after the last treatment 3 of these were less than one year old and the fourth was thirteen months old on admission The two-year cure rate for the various methods of treatment is given in Table 2

Case reports

Case 1 Boy aged 9 months who in November 1966 underwent right nephrectomy and ureterectomy for nephroblastoma twice the size of a man s fist the left kidney appeared to be normal Cyclophosphamide was given on the day of the operation and on each of the next 9 days together with 2 500 rad to the tumour bed over a period of four weeks Haematuria occurred in June 1967 Surgical exploration after inconclusive urography revealed no neoplasm Exploration in November 1967 after another episode of haematuria disclosed a growth in the upper lobe and two tumours in the central part of the left kidney Partial resection of the left kidney was followed by a course of cyclophosphamide More than two years after the last treatment the patient was without signs of a neoplasm or impaired renal functions

Case 2 Boy aged 11 months Exploratory laparotomy in September 1963 confirmed the clinical diagnosis of bilateral nephroblastoma with lymph node metastases Treatment consisted of 2 000 rad over four weeks to the left kidney and 1 000 rad over two weeks to the right kidney with actinomycin D the latter repeated every two months In June 1964 a recurrence in the left kidney initiated approximately 1 100 rad to the left and 2 300 rad to the right kidney In January 1965 the residual mass was partially resected from the left kidney and actinomycin D given for six consecutive days Another 1 000 rad was delivered to both kidneys over a period of one week In August 1965 complete failure of the left

Table 3

Fifteen patients with bilateral nephroblastoma treated during the period 1943—1967

Sex	Age	First sign	Date of diagnosis	Stage at first treatment	Treatment	Death: Date	Death: Stage
♂	10 mos	Abdominal swelling	June 1943	Left — Right Fixation inoperable	None	Nov 1943	Primary tumour bilat No metastases
♀	4 mos	Abdominal swelling	Nov 1964 Dec 1965	Left Pulmonary metastases Right Encapsulated	Irradiation 1500 rad Actinomycin D Nephrectomy + irradiation (dose unknown)	Feb 1965	Primary tumour left Metastases
♀	5 yrs	Haematuria	Sept 1958	Left Lymph node metastases Right Extension beyond the capsule and invasion of vessels	Nephrectomy + irradiation 1500 rad Resection	Jan 1959	? Primary tumour No mestastases
♂	7 mos	Abdominal swelling	Dec 1958	Left — Right —	None	Jan 1959	Primary tumour bilat No metastases
♂	6 mos	Abdominal swelling	Dec 1959	Left Encapsulated Right Invasion of vessel	Nephrectomy + irradiation 1500 rad Resection (not radical)	Jan 1961	Primary tumour right No metastases
♀	3 yrs	Haematuria	Sept 1959 Feb 1959	Left Pulmonary mestastases Right Encapsulated	Irradiation 2500 rad Nephrectomy + irradiation 1500 rad	June 1960	Primary tumour left ? Metastases
♀	3 yrs	Haematuria	March 19[illegible]9	Left Invasion of vessels Right Fixation inoperable	Nephrectomy + irradiation 2200 rad Actinomycin D Biopsy + irradiation 2[illegible]00 rad Actinomycin D	Dec 1959	Primary tumour bilat Metastases
♂	7 mos	Abdominal swelling + haematuria	Sept 1960	Left Encapsulated Right Encapsulated	Resection + irradiation 1900 rad Nephrectomy	April 1962	Primary tumour left No metastases

Table 3 *(cont.)*

Sex	Age	First sign	Date of diagnosis	Stage at first treatment	Treatment	Death: Date	Death: Stage
♀	3 yrs	Abdominal swelling	Sept 1963	Left Extension beyond the capsule Right —	Nephrectomy None	Feb 1964	Primary tumour right Metastases
♀	11 mos	Abdominal swelling	Oct 1960	Left Encapsulated Right Invasion of vessel	Resection Irradiation 1300 rad nephrectomy + irradiation 1000 rad	Oct 1961	Primary tumour left Metastases
♂	4 yrs	Abdominal swelling	April 1962	Left Encapsulated Right Burst at operation	Nephrectomy + irradiation 1500 rad Resection	March 1963	Primary tumour bilat Metastases
♂	10 mos	Abdominal swelling + haematuria	Feb 1964	Left Invasion of vessels Right Fixation inoperable	Nephrectomy + irradiation 2000 rad Actinomycin D Biopsy + irradiation 2000 rad Actinomycin D	Sept 1965	? Primary tumour Metastases
	4 yrs	Abdominal swelling	Dec 1965	Left Invasion of vessels lymph node metastases Right —	Nephrectomy + Actinomycin D Actinomycin D	Dec 1965	Primary tumour right No mestatases Died at operation
	4 yrs	Abdominal swelling	May 1965 July 1964	Left Lymph node and pulmonary metastases Right Invasion of vessels	Irradiation 2800 rad resection Vincristine Nephrectomy + irradiation 2000 rad Actinomycin D	May 1966	Primary tumour left Metastases
	7 mos	Abdominal swelling	March 1967	Left Generalized disease Right —	Irradiation 1000 rad nephrectomy Actinomycin D Resection + Actinomycin D	May 1967	Primary tumour right Metastases

kidney necessitated nephrectomy The last follow up performed in March 1970 revealed no evidence of a neoplasm or of renal failure (Previously published 13 27)

Case 3 Boy, aged 13 months in whom bilateral nephroblastoma was treated by partial resection of both kidneys the right tumour was encapsulated and the left penetrated the capsule and invaded the vessels Actinomycin D was given on the day of the operation and during the next six days A total of 2 000 and 1 500 rad was delivered to the right and left tumour bed regions respectively over a period of four weeks Left nephrectomy was performed for recurrent tumour ten months later Oncovin was administered (1 mg weekly) during the next seven weeks About a year from this second operation there was no evidence of a growth or of impaired renal function (Previously published 13 27)

Case 4 Boy aged 1 year, who in 1960 had had right nephrectomy for a nephroblastoma followed by about 2 000 rad to the tumour bed An abdominal swelling was palpated in the region of the left kidney in 1966 and after irradiation with a tissue dose of about 1 800 rad partially resected The tumour was encapsulated Actinomycin D and cyclophosphamide medication were administered at regular intervals for about a year Two years after the last treatment the boy was well and there were no signs of recurrence metastases or impairment of renal function (Previously published 13 27)

More detailed data relating to the non survivors are presented in Table 3

There were local recurrences in all 5 patients in whom no postoperative irradiation was applied to the tumour bed and in 6 of the 15 patients in whom irradiation was administered, in 3 after irradiation only (2 200, 2 500 and 1 500 + 1 500 rad) and in 3 patients after resection and postoperative irradiation (2 000, 1 500 and 1 900 rad) The doses to the cured patients were 2 500, 2 000, 4 300 and 1 800 rad

One patient died at operation, and in another the stage at death was not known In 6 of the remaining 13 patients the clinical findings suggested that the primary tumour and renal insufficiency were the cause of death, at autopsy the renal outflow tract was obstructed by the growth and no distant metastases were evident Autopsy in one patient disclosed metastases in the lungs, pleura, liver and cerebellum and a primary growth in one kidney Distant metastases were present in 8 patients in whom no autopsy was performed, in 3 patients the stage of the primary growth at death was not known No patient died from renal insufficiency unless there was local recurrence of the neoplasm

Discussion

Eleven of the 19 patients comprising this material were less than one year old on admission (57 per cent) The peak incidence of nephroblastoma occurred at 2 years The low age of the patients with the condition, its occasional observation at birth and the relatively high frequency of associated congenital malformation of the urogenital tract point to a foetal origin of the neoplasm If some

measure of immunologic dependence of this kind of tumour is assumed it would seem reasonable to ascribe the relatively high incidence of bilateral involvement in this age group to the established low level of the immunologic protection in children below one year of age

While the difficulty of distinguishing between primary bilateral nephroblastoma and a unilateral growth that has spread to the other kidney is recognized (7 12 16 21 25 26), the clinical problems presented by the two conditions are roughly the same and the two types have therefore been considered as a single group

The low incidence of bilateral anomalies should always suggest neoplasms as has been pointed out elsewhere (1, 26) Quite a long period elapsed before a diagnosis of malformation was corrected in 3 of the present cases of bilateral nephroblastoma

The more aggressive treatment of this condition given in the last decade has yielded better results (9 31) and in recent years there has been a greater number of survivors with bilateral involvement (1 2 23) Six children of the present material died from local damage caused by the primary growth (there were no metastases) with more energetic treatment at least some of these lives might have been saved

A compromise between radical removal of the neoplasm and preservation of renal function must be sought before deciding the treatment to be given in bilateral cases Few cures have been secured by operation alone (8 11 13) and surgery combined with radiation is the treatment of choice The effect of actinomycin D on the cure rate has yet to be conclusively established (29 30) Partial nephrectomy may be as effective as total nephrectomy with encapsulated tumours (8 13 28) The radiation dose required in bilateral growths is also uncertain The tolerance of the kidney in children has yet to be ascertained (15 22 32) Some relevant figures have been reported for 6 children (17) in whom nephrectomy was followed by irradiation with doses of more than 2 400 rad and who died from renal failure due to radiation nephritis Doses higher than 2 000 rad have been reported to cause radiation nephritis (6 19) Recurrences were observed in the present series after irradiation with doses above 2 000 rad On the other hand one patient given 4 300 rad to both kidneys still had no evidence of renal failure 3 years later there are however reports of this sequela developing through radiation nephritis as long as twenty years after treatment (14 15 18) The results for the present material throw no light on this matter

The value of preoperative radiotherapy is difficult to establish even in quite large series (24) Of 4 patients with bilateral tumours so treated 2 were cured and 2 died (One of these had metastases on admission) It would seem that the value of preoperative irradiation in diminishing the growth and facilitating

the surgical procedure is even greater in the bilateral conditions, these of cours present more severe surgical problems, quite apart from the potential reductio in the number of metastases For 2 out of 4 surviving patients the treatmen consisted in combined bilateral surgery and irradiation, for another survivo partial nephrectomy on one side and bilateral irradiation with high doses, an for the fourth (cured) partial resection 6 years after nephrectomy and irradia tion for the primary tumour, all 4 patients received chemotherapy A combina tion of surgery and irradiation of both kidneys would seem to be the metho of choice *The appropriate surgical procedure must be chosen individually* Since actinomycin D has not been found to impair renal function there would appea to be nothing against its employment (17)

The fact that the results were better for the afflicted children under 1 year o age than for the older ones cannot be easily explained since it is not know whether a specific immunologic response may be more easily induced in infants

Acknowledgement

The author takes this opportunity of thanking Prof M Sulamaa and Prof L Holst (Helsinki) and Dr O Knutrud (Oslo) as well as her Swedish colleagues who have made their files available Prof N O Ericsson and Dr I Ahstrom are thanked for their advice and support *This investigation was supported by the Swedish Cancer Society*

SUMMARY

A series of 19 patients with bilateral nephroblastoma is presented and some clinical features of the condition its treatment and the outcome are discussed The treatment of choice would seem to be radical removal of the two tumours followed by radiotherapy The role of chemotherapy could not be established

ZUSAMMENFASSUNG

Eine Serie von 19 Patienten mit bilateralem Nephroblastom wird hinsichtlich der kli nischen Erscheinung dieser Krankheit und deren Behandlung und Prognose diskutiert Die Methode der Wahl scheint radikale Exstirpation der beiden Tumoren mit nachfolgender Bestrahlung zu sein Über den Wert der Chemotherapie konnte kein Urteil abgegeben wer den

RÉSUMÉ

L auteur presente une serie de 19 malades atteints de nephroblastome bilateral et exa mine certains des caracteres cliniques de cette affection son traitement et son pronostic Le traitement de choix semble etre l exerèse radicale des deux tumeurs suivie de radiothérapie Le role de la chimiothérapie n a pas pu etre établi

REFERENCES

1 ANDERSON F E HARPER J M SMALL M P and ATTWELL W H Bilateral diffuse Wilms tumor A five year survival J Urol 99 (1968) 707

2 — HERLONG J H HARPER J M et coll Bilateral Wilms tumor Diagnosis and management Clin Pediat 7 (1968) 596

3 BISHOP H C and HOPE J W Bilateral Wilms tumors J pediat Surg 1 (1966) 476

4 CLOSE M B PETERSON C A and JOHNSON R P Bilateral embryoma of the kidney Patient alive and well three years after treatment Radiology 67 (1956) 99

5 COCHRAN W and FROGATT P Bilateral nephroblastoma in two sisters J Urol 97 (1967) 216

6 COGAN S R and RITTER I I Radiation nephritis clinopathologic correlation of three surviving cases Amer J Med 24 (1958) 530

7 FALKINBURG R W KAY M and SAYER E A Recurrence of nephroblastoma (Wilms tumor) eight years after nephrectomy J Amer med Ass 155 (1954) 1228

8 FLANNERY J L Survival after nephrectomy and partial nephrectomy for bilateral Wilms tumors U S armed Forces med J 9 (1958) 561

9 GARRETT R A DONOHUE J P and ARNOLD T Metastatic renal embryoma Survival following therapy J Urol 98 (1967) 444

10 GOLDBERG L G and DIAZ A Bilateral Wilms tumor J Urol 86 (1961) 211

11 GROSS R E and NEUHAUSER E B D Treatment of mixed tumors of the kidney in childhood Pediatrics 6 (1950) 843

12 JAGASIA K H THURMAN W G PICKETT E and GRABSTALDT H Bilateral Wilms tumors in children J Pediat 65 (1964) 371

13 JEREB B AHSTROM L and ERICSSON N O Nephroblastoma Results of treatment 1927—1967 (A study of 95 patients admitted to Radiumhemmet) Z Kinderchir Grenzgeb Suppl to 6 (1969) 165

14 LUXTON R W Clinical and pathological effects of renal irradiation In Progress in radiation therapy p 15 Edited by F Buschke Grune & Stratton New York 1962

15 — and KUNKLER P B Radiation nephritis Acta radiol Ther Phys Biol 2 (1964) 169

16 MARTIN L W and KLOECKER R J Bilateral nephroblastoma (Wilms tumor) Pediatrics 28 (1961) 101

17 MITUS A TEFFT M and FELLERS F X Long term follow up of renal functions of 108 children who underwent nephrectomy for malignant disease Pediatrics 44 (1969) 912

18 O MALLEY B D ANGIO G J and VAWTER G F Late effects of roentgen therapy given in infancy Amer J Roentgenol 89 (1963) 1067

19 PATERSON R Renal damage from radiation during treatment of seminoma testis J Fac Radiol 3 (1952) 270

20 RICKHAM P P Bilateral Wilms tumour Brit J Surg 44 (1957) 492

21 RITTER J A and SCOTT E S Embryoma of contralateral kidney ten years following nephrectomy for Wilms tumor J Pediat 34 (1949) 753

22 RUBIN P and CASARETT G W Clinical Radiation Pathology Vol 1 chapter 8 p 293 W B Saunders Philadephia London and Toronto 1968

23 SCHAMBER D T and VAN BUSKIRK K E Bilateral Wilms tumor Milit Med 130 (1965) 1009

24 SCHWEISGUTH O GUY E et SENTENAC J P La place de la radiotherapie dans le traitement du néphroblastome de l enfant J Radiol Électrol 46 (1965) 377

25 SCOTT L S Bilateral Wilms tumour Brit J Surg 42 (1955) 513

26 SHEACH J M Bilateral Wilms tumour A case report with a review of the literature Brit J Urol 25 (1954), 109
27 SIROLA K Behandlungsresultate von Wilms Tumoren mit besonderer Berucksichtigung der Lungmetastasen und bilateraler Tumoren Z Kinderchir Grenzgeb Suppl to 6 (1969) 183
28 STEIN J J and GOODWIN W F Bilateral Wilms tumor including report of a patient surviving ten years after treatment Amer J Roentgenol 96 (1966) 626
29 SUKAROCHANA K and KIESEWETTER W B Wilms tumor Factors influencing long term survival J Pediat 69 (1966) 747
30 SULLIVAN M P Curable metastatic tumors of childhood Tex St J Med 61 (1965) 800
31 SWENSON O and BRENNER R Aggressive approach to the treatment of Wilms tumor Ann Surg 166 (1967), 657
32 VAETH J M The remaining kidney in irradiated survivors of Wilms tumor Amer J Roentgenol 92 (1964) 148

FROM THE DEPARTMENT OF EXPERIMENTAL RADIOLOGY, FACULTY OF MEDICINE
KYOTO UNIVERSITY, KYOTO JAPAN

INDIVIDUAL DIFFERENCES IN RADIOSENSITIVITY OF MICE CORRELATED WITH THEIR METABOLIC RATE

by

Y UENO

The relationship between metabolic rate and recovery half time described by MICHAELSON & ODLAND (1962) suggests that the metabolic rate is one of the factors involved in the species difference in radiosensitivity among mammals and is related mainly to the process of recovery from radiation injury If the relationship can be extended from the species difference in radiosensitivity to individual differences among mammals of the same species individual differences in radiosensitivity may be explained on the basis of differences in metabolic rates The present work was planned to investigate this possibility

Experimental procedures Ninety day old male and female DBA/2 mice were housed for 30 days before the start of the experiments in the animal room in order to become adapted to the conditions The mice were given water and Funabashi Farm s chow ad libitum Aureomycin powder (4 g/l) was added to the water after irradiation it had been proved in a preliminary experiment that this amount of aureomycin powder has no effect on the production of endogenous spleen colonies The animal room was kept at 20 ± 2 C

Submitted for publication 29 June 1970

level in vivo and the whole body level, as compared with the mice with high or low metabolic activity

The relationship between radiosensitivity and metabolic activity presented in previous reports (BLOUNT & SMITH 1949, SMITH et coll 1949, KIMELDORF et coll 1950, SMITH & SMITH 1951, TSUCHIYA et coll 1963) is that an increase in metabolic activity is always accompanied with an increase in radiosensitivity in mammals However, it has also been found that an increase in metabolic rate is accompanied by an acceleration of the recovery process (MICHAELSON & ODLAND 1962, CASARRET 1969, WILSON 1969) The former relationship corresponds to that observed in groups C and D and the latter to that in groups A and B Thus, the relationship between metabolic rate and radiosensitivity presented here can be analyzed into two components one the effect of the metabolic rate on accelerating the injury process due to irradiation, and the other the acceleration of the recovery process The relationship observed between metabolic rate and radiosensitivity is an index of a balance between the two components In mice with a comparatively low metabolic rate, the effect of the metabolic rate on accelerating the recovery process must play the main role, and its effect on accelerating the injury process must constitute the means in mice with comparatively high radiosensitivity An optimal metabolic rate in a population of mammals for the suppression of radiosensitivity therefore appears evident Such consideration of balance has been reported (POSPISIL & NOVAK 1959, UENO 1968) and has been expressed mathematically as an imbalance of metabolic energy processes (NOVAK et coll 1964)

The problem of how the metabolic rate accelerates the recovery process in mice with a comparatively low metabolic rate and how it accelerates the injury process in mice with a comparatively high metabolic rate remains to be solved

Both sexes were used in the present experiment If the male female ratio in each group were not similar, the present data might suggest that radiosensitivity depends on sex The ratios were similar in the four groups The data seem to indicate that differences in radiosensitivity depend on the metabolic rate

Mice with comparatively low radiosensitivity appear to have a relatively large number of ESC which seem to be composed mainly of erythropoietic cells The main factor in the so called bone marrow death after irradiation with the doses used in the present experiment is said by PATT (1969) to be granulocytopenia Though histologic examinations of ESC were not carried out in the present research, there may be differences in the ratio of myelocytic ESC to erythrocytic ESC depending on the metabolic rates of the host mice, in addition to the differences in numbers of ESC in the myelocytic or erythrocytic

system. At any rate, the number of ESC forming stem cells closely related to bone marrow death is large in the mice with an optimal metabolic rate. This suggests that the optimal metabolic rate of the host mammal stimulates the production of many hemopoietic stem cells or reduces the radiosensitivity of each stem cell. If the latter mechanism is obtained, the optimal metabolic rate may stimulate stem cells to develop from less to more differentiated stages. The present data indicate the possibility that one of the mechanisms by which the metabolic rate modifies the radiosensitivity of an individual mouse at the whole body level is via the dynamics of the hemopoietic system. This possibility is also recognized in investigations on species or strain differences in radiosensitivity in mammals (TSUCHIYA et coll. 1969, FLIEDNER 1969).

Acknowledgements

The author wishes to thank Miss S. Iwase and Miss M. Maeda for their technical assistance.

SUMMARY

The survival times, survival rates and endogenous spleen colony counts were correlated with the metabolic rates of DBA/2 male and female mice. The radiosensitivity of individual mice with low or high metabolic rates was greater than that of mice with intermediate metabolic rates in the same population; this was apparent at both whole body and cellular levels.

ZUSAMMENFASSUNG

Die Überlebenszeiten, die Überlebensraten und die Zahlen der endogenen Milzkolonien wurden zur Grösse des Metabolismus von männlichen und weiblichen DBA/2 Mäusen korreliert. Die Strahlenempfindlichkeit individueller Mäuse mit niedrigen oder hohem Metabolismus war grösser als von Tieren derselben Population mit mittleren Metabolismus; das galt sowohl für den Gesamtorganismus als auch für das zelluläre Niveau.

RÉSUMÉ

L'auteur a établi une corrélation entre les taux métaboliques de souris mâles et femelles DBA/2 et le temps de survie, le taux de survie et la numération des colonies spléniques endogènes. Dans une même population, la radiosensibilité de certaines souris ayant des taux métaboliques bas ou élevés est plus grande que celle des souris qui ont des taux métaboliques moyens; ceci apparaît aussi bien au niveau du corps entier que des cellules.

REFERENCES

BLOUNT JR H C and SMITH W W The influence of thyroid and thiouracil on mice exposed to roentgen radiation Science 109 (1949), 83

CASARRET G W Patterns of recovery from large single dose *In* Comparative cellular and species radiosensitivity First edition p 42 Igaku Shoin Tokyo 1969

FLIEDNER T M A cytokinetic comparison of hematological consequences of radiation exposure in different mammalian species *In* Comparative cellular and species radiosensitivity First edition p 89 Igaku Shoin Tokyo 1969

KIMELDORF D J JONES D C and FISHLER M C The effect of exercise upon the lethality of roentgen rays for rats Science 112 (1950) 175

MICHAELSON S M and ODLAND L T Relationship between metabolic rate and recovery from radiation injury Radiat Res 16 (1962), 281

NOVAK L POSPISIL M and HOSEK B Relationship of radiosensitivity to the rate of growth Folia biol (Praha) 11 (1965) 147

PATT H M Species differences in leukocyte restoration after irradiation *In* Comparative cellular and species radiosensitivity First edition p 112 Igaku Shoin Tokyo 1969

POSPISIL M and NOVAK L Importance of the type of metabolism for the radiosensitivity of mice Nature 184 (1959) 1814

SMITH W W HICHMAN B J MITCHELL J R and BLOUNT JR H C Effect of environmental temperature on the response of mice to whole body roentgen radiation Proc Soc exp Biol Med 71 (1949) 498

— and SMITH F Effect of thyroid hormone on radiation lethality Amer J Physiol 165 (1951) 639

TSUCHIYA T HAYAKAWA J MURAMATSU S et coll Radiosensitivity and thyroid function in mice Radiat Res 19 (1963), 316

— — TAMANOI I et coll The difference in erythoropoietic recovery after irradiation in two strains of mice *In* Comparative cellular and species radiosensitivity First edition p 53 Igaku Shoin Tokyo 1969

UENO Y Diurnal rhythmicity in the sensitivity of hemopoietic cells to whole body irradiation of mice Int J radiat Biol 14 (1968) 307

— The radiosensitivity of mammals on the whole body level (In Japanese) *In* Radiation cellular biology First edition p 472 Asakura Shoten Tokyo 1968

— Prediction of interindividual differences in radiosensitivity in mammals *In* Life sciences and space research VII First edition p 210 North Holland Publ Co Amsterdam 1969

WILSON B R *In* Comparative cellular and species radiosensitivity First edition p 281 Igaku Shoin Tokyo 1969

FROM KODAK AB THE DEPARTMENT OF DIAGNOSTIC RADIOLOGY (DIRECTOR PROF B NORDENSTROM), KAROLINSKA SJUKHUSET AND THE DEPARTMENT OF CLINICAL RADIOPHYSICS (DIRECTOR PROF R WALSTAM) THE NATIONAL INSTITUTE OF RADIATION PROTECTION STOCKHOLM SWEDEN

DIRECT BEAM CONTROL IN RADIOTHERAPY WITH HIGH ENERGY PHOTONS

by

L Jevbratt C Lagergren and B Sarby

Controls performed directly with a therapy beam instead of a separate roentgen simulator eliminate uncertainties in the repositioning of the patient between the simulator and the therapy unit The position of the beam in relation to the anatomic structures will also be ascertained more precisely Moreover shielding blocks for radiosensitive organs such as the spinal cord kidneys and eyes will be placed more accurately and the margins to these organs reduced A method of direct beam control is particulary valuable when high energy roentgen radiation from linear accelerators and betatrons is used since the well defined beam of the units will be exploited for precise tumor treatment

The difficulty of employing the therapy beam for roentgenography at high photon energies is due to the small difference in the mass absorption coefficients of bone and soft tissues The radiation contrast in the traversing beam will be due chiefly to variations in tissue density in the irradiated volume implying a consequent reduction in the image contrast in the roentgenogram In spite of this

Submitted for publication 30 June 1970

Fig. 1. Characteristic curves for various types of film irradiated with 6 MV roentgen radiation. Left to right at exposure axis: Fuji Medical Diagnostic Film, Kodak Microtex, Gevaert N 51, Kodak Phototypesetting, Kodalith Royal Ortho and Kodalith Ortho Type 3.

difficulty it has still been possible to utilize the direct therapy beam by applying metal indicators or gas as contrast media to produce interpretable control films. This technique has been applied in earlier investigations either with photographic film (LINDELL & WALSTAM 1956, FRISCHBIER & KUTTIG 1960, PERRYMAN et coll. 1960, TASKINEN & VAHATALO 1968) or with special image intensifier systems (MALVEN et coll. 1968). As early as 1945 MERMAGEN described a 1 MV human chest roentgenogram and later TUDDENHAM et coll. (1953) reported that super voltage roentgenographic technique would increase the diagnostic value of chest roentgenograms.

The recent introduction of a new cobalt 60 unit (Siemens Gammatron 3), a 6 MeV linear accelerator (Varian) and a 42 MeV betatron (Siemens) at Radium hemmet has made direct and rapid beam control all the more desirable. The results of trials of the above methods were often most difficult to interpret at the high photon energies from the accelerators. The present investigation was accordingly undertaken with a view to increasing the contrast in the beam control images by finding the optimal film, exposure conditions and processing parameters.

Method. A number of diagnostic films, low sensitivity industrial films and graphic films were irradiated for a number of exposures with 6 MV roentgen radiation in order to compare their properties. The processing procedure for the respective films was adjusted individually in accordance with the manufacturers' instructions for maximum contrast. The slope of the characteristic curve

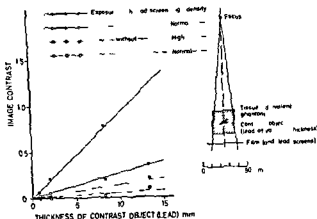


Fig 2 Image contrast at high (3 5 to 4 0) and normal density (1 0 to 1 5) on Kodak Microtex film in recording of metal absorbers of different thicknesses in a tissue equivalent phantom The image contrast is determined by the differences in density of the film beside and behind the contrast object The exposures were performed with 6 MV roentgen radiation with the films either between lead screens or in a paper envelope

increased at high densities for the industrial film (Fig 1) The slope for the other films decreased at high densities The maximum film contrast γ represented by the maximum slope of the curves was 1 7 for the diagnostic film and 6 5 for the industrial film while for graphic film it ranged from 3 5 to 12 The most suitable film judged from contrast properties was the low sensitivity industrial film with $\gamma = 6\ 5$ or graphic film with $\gamma = 12$ The industrial film Kodak Microtex was chosen for the subsequent work primarily because of its more suitable exposure range (latitude) and sensitivity compared to the graphic film as regards the magnitude of the daily treatment doses Industrial film can also be processed automatically in the developing machine (Kodak Versamat 317) for diagnostic films while graphic film must be developed manually

The films in Fig 1 were placed during irradiation between polished lead screens 2 mm thick a value found to be suitable at all the relevant beam energies The purpose of these is to produce Compton electrons and characteristic radiation to blacken the film and to absorb oblique secondary electrons and scattered photons from the patient. The value of the lead screens was examined by an experiment depicted schematically in Fig 2 Pieces of metal of different thickness were placed in the middle of a homogeneous phantom which was irradiated with 6 MV roentgen radiation The recording on the Kodak Microtex



Fig. 3. Skull phantom exposed with a) simulator (65 kV), b) gamma radiation from a cobalt unit, *c) 6 MV roentgen radiation from a linear accelerator and d)* 42 MV roentgen radiation from a betatron. The film exposed with ^{60}Co radiation (b) has the best contrast of those obtained with the therapy units but the large diameter of the source (2 cm) produces considerable geometric blur. *Owing to the higher radiation energies the contrast is slightly poorer* for the 6 and 42 MV roentgen (c) and (d) than for the ^{60}Co radiation (b) but the definition is better because of the smaller focus (2 mm).



Fig 4 Carcinoma of the lung a) Diagnostic roentgenogram b) Beam control film exposed with the linear accelerator for 3 sec The extent of the tumour is clearly evident in the roentgenogram exposed in the therapy beam



Fig 5 Carcinoma of the lung a) Diagnostic roentgenogram b) Beam control film exposed with the linear accelerator for 3 sec

film was considerably greater for the films exposed in contact with the lead screens than for those enclosed in paper envelopes

The best image quality is obtained by a heavy exposure because the contrast of industrial film increases with density (Figs 1 and 2) By producing contact



Fig. 6. Nasopharyngeal carcinoma. a) Control of a lateral beam with the simulator. b) Corresponding control with linear accelerator beam. Poor agreement between the beams of the accelerator and the simulator, even though the films were taken in close succession.

copies of the roentgenogram on duplicate film; however, an image with normal density but still the same contrast can readily be obtained. A further increase in the contrast of the original image may be produced if required by means of contact copies on a graphic film. For routine work, however, it suffices to examine the heavily exposed roentgenogram under a high intensity illuminator.

A tissue equivalent skull phantom was exposed with gamma radiation from the cobalt unit, 6 MV roentgen radiation from the linear accelerator and 42 MV roentgen radiation from the betatron to examine the recording of the various structures on the low sensitivity industrial film at the relevant radiation energies. The films, together with the corresponding roentgenogram obtained with the simulator (65 kV), are presented in Fig. 3. The film exposed with the cobalt unit had the best contrast of the roentgenograms obtained with the therapy units, but due to the large source diameter (2 cm) it was geometrically blurred. The roentgenograms exposed with the linear accelerator and betatron had slightly poorer contrast because of the higher radiation energies, but were sharper because of the smaller foci (about 2 mm). In all these cases, however, the film always registers a variation in tissue absorption large enough to permit anatomic details to be examined without the aid of indicators.

Discussion

TASKINEN & VAHATALO (1968) have pointed out that it is desirable to expose the beam control film throughout the whole treatment time. At high energy photon radiation, when the differences in mass absorption coefficient of different tissues are small, this point of view is however difficult to fulfil if roentgenograms of sufficient high image contrast are required, depending on the contrast and the



Fig 7 Chordoma of the atlas and epistropheus with destruction (arrows) A film exposed with the betatron 42 MV roentgen radiation for control of a lateral beam The anatomic details appear clearly enough to define the position of the beam



a



b

Fig 8 Sternberg's disease a) Simulator film in which the contour of the kidneys has been marked after injection of contrast medium b) Beam control obtained with the linear accelerator with the kidney protecting block in correct position The vertebrae are clearly enough reproduced to define the position of the therapy beam

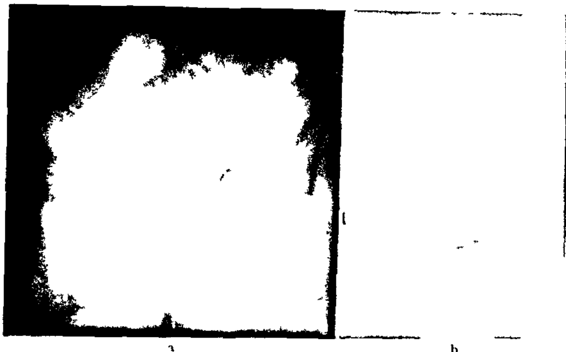


Fig. 9. Carcinoma of urinary bladder. *Direct beam control films exposed with the linear accelerator* with about 30 ml carbon dioxide in the bladder. a) Control of a beam from behind. b) Control of a wedge filter beam at 60° angle of incidence to the sagittal plane.

latitude of a film being reciprocal quantities. Moreover it can be an advantage as in ordinary diagnostic examinations, to employ short exposure times, i.e. obtained with films of high sensitivity in order to counteract blur due to movement. A suitable density of the industrial film is obtained by a dose of 5 to 20 rad to the patient; this requires an irradiation time of 1 to 5 seconds, which is short enough for the patient to be able to hold his breath. This is particularly important at beam controls of malignant processes located in the lungs and abdominal organs (Figs. 4 and 5). *It is also advisable to use short exposures when there are difficulties* in reproducing the position of the patient in the therapy beam from one treatment to another, e.g. in the treatment of cranial tumours. A rapid check of the beam may then be carried out and any adjustment required made before the therapeutic irradiation is started. This kind of beam control requires however that the position of the patient on the treatment table is fixed *throughout* the whole treatment time.

The advantage of direct beam control is illustrated in Fig. 6, which represents control of a lateral beam for the treatment of nasopharyngeal carcinoma. A surprisingly poor coincidence appears between the beams of the therapy unit and the roentgen simulator, in spite of the fact that the films were *taken in close* succession. The deviation is partly due more to lower mechanical accuracy of the

simulator (JUNG et coll. 1968) than to the linear accelerator. The correspondence between the roentgen beam and the light beam localizing system is also lower for the simulator. Of less significance is the difficulty in reproducing the patient position from one exposure to another, in particular when the patient is fixed by a plastic mould.

The great difference in the density of air and tissue enhances the demonstration of pathologic changes in the lungs and mediastinum extremely well in roentgenograms exposed with high energy photons. The better impression of the extent of the tumour in films obtained with the linear accelerator than with diagnostic radiation is evident from Figs. 4 and 5. Irradiations with beams that have traversed bony structures record these clearly; they may therefore serve as reference points for estimating the position of the therapy beam (Figs. 7 and 8). The position of the shielding block for radiosensitive organs may also be accurately controlled.

The difference in absorption between gas and tissue in direct beam control of tumours of the urinary bladder may be exploited by injecting a suitable amount of carbon dioxide (about 30 ml) into the bladder just before the exposure is made (Fig. 9). One advantage of carbon dioxide over air is that air embolism is avoided (BARTLEY & HELANDER 1960). The risk of infection may be minimized by injection of the gas through a millipore filter (Swinnex).

Direct beam controls have been performed routinely for the last two years in the case of treatment with the cobalt unit, the linear accelerator and the betatron. As is evident from the above examples, the method has proved very valuable for different techniques of tumour irradiation.

SUMMARY

It is an advantage to be able to perform set-up controls directly with the therapy beam in the precise radiotherapy of deep-lying tumours with a cobalt unit, linear accelerator or betatron. A special photographic method has been evolved by means of which this is possible. Examples are given of radiotherapy techniques in which the method has proved particularly valuable; it is very suitable for routine beam controls.

ZUSAMMENFASSUNG

Es ist ein Vorteil, direkt Kontrollbilder mit dem Therapiestrahl bei der genauen Radiotherapie von tiefliegenden Tumoren mit einer Cobalt-Einheit, einem linearen Accelerator oder einem Betatron durchführen zu können. Es wurde eine spezielle photographische Methode entwickelt, mit deren Hilfe dieses möglich ist. Es werden Beispiele für radiotherapeutische Techniken gegeben, bei denen sich diese Methode als besonders wertvoll erwiesen hat; diese ist auch für routinemässige Strahlengangkontrollen sehr brauchbar.

RÉSUMÉ

Il est avantageux de pouvoir controler directement la mise en place du sujet par le faisceau de radiotherapie dans la radiotherapie precise de tumeurs situees en profondeur avec une unite de colbalt therapie un accelerateur linéaire ou un betatron Les auteurs ont mis au point une methode photographique speciale qui permet ce controle de mise en place Ils donnent des exemples de techniques radiotherapiques dans lesquelles cette methode s est montre particulierement utile Elle convient très bien pour le controle systematique des faisceaux d irradiation

REFERENCES

BARTLEY O and HELANDER C G Double contrast cystography in tumours of the urinary bladder Acta radiol 54 (1960) 161

FRISCHBIER H J und KUTTIG H Zur Technik der direkten Feldkontrollaufnahme mit der Telekobalttherapieeinheit Strahlentherapie 113 (1960) 610

JUNG B LARSSON B ROSENGREN B et coll Roentgen stand for field positioning in high energy radiotherapy Acta radiol Ther Phys Biol 7 (1968) 282

LINDELL B and WALSTAM R A new telegamma apparatus Acta radiol 45 (1956) 255

MALKEN R ROSENGREN B and WALLMAN H Field control in roentgen therapy with a 5 MeV linear accelerator by means of television Acta radiol Ther Phys Biol 7 (1968) 467

MERMAGEN H Million volt chest radiograph Radiogr clin Photogr 21 (1945) 68

PERRYMAN C R MCALLISTER J D and BURWELL J A Cobalt 60 radiography Amer J Roentgenol 83 (1960) 525

TASKINEN P J und VAHATALO S Feldkontrolle mit Kobalt 60 gammastrahlen wahrend der gesamten Bestrahlungszeit Strahlentherapie 136 (1968) 557

TUDDENHAM W J HALE J and PENDERGRASS E P Supervoltage diagnostic roentgenography Amer J Roentgenol 70 (1953) 759

FROM THE RADIATION PHYSICS DEPARTMENT (DIRECTOR PROF G HETTINGER),
UNIVERSITY OF UMEÅ SWEDEN

INFLUENCE OF SCATTERING FOILS, TRANSMISSION MONITORS AND COLLIMATING SYSTEM ON THE ABSORBED DOSE DISTRIBUTION FROM 10 TO 35 MeV ELECTRON RADIATION

by

H SVENSSON

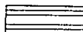
To flatten the radiation fields of medical betatrons scattering foils are inserted into the electron beam There are however, also other scattering materials in the beam e g accelerator tube window transmission chambers and air Electrons are also spread from the walls of the collimator into the central beam The complete scattering system influences the shape of the depth dose curves the maximum absorbed dose rate at treatment distance, and the flattening of the treatment fields The present investigation was performed in order to improve the scattering geometry and the field size defining system of a 35 MeV Brown Boveri (BBC) Asklepitron Special importance was given to the improvement of the flattening of the radiation fields

Homogeneity of the treatment fields

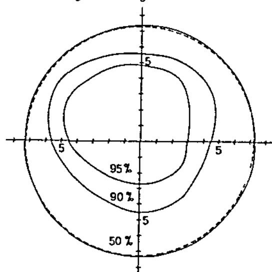
SVENSSON & HETTINGER (1971) demonstrated in an investigation with 11 betatrons in the Nordic countries that the flattening of the radiation fields was very poor with electron radiation The authors measured the flattening in a plane

Submitted for publication 22 October 1970

Original foil for energies up to 25 MeV
(Maximum thickness 0.4 mm Cu)



Resulting flattening



Modified foil for energies up to 29 MeV
(Uniform thickness 0.1 mm Ag)



Resulting flattening

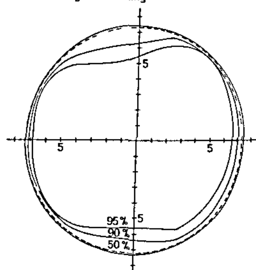


Fig 1 Flattening of the electron beam with different scattering foils The isodensity curves were measured from films irradiated perpendicularly to the electron beam in a polystyrene phantom at 2 cm depth The irradiation geometry is shown in fig 2b The field size was Ø 14.5 cm

perpendicular to the beam with photographic films at 2 cm depth in a polystyrene phantom The ratio between the area inside the 80 % isodensity curve and the geometric field size was defined as a homogeneity index The geometric field area was taken as that defined by the collimator or by the light field on the phantom surface The homogeneity index with the BBC betatrons investigated was on an average 0.6 The homogeneity index is affected by the accelerator tube window, absorbed dose monitor, balancing chamber and collimating system as discussed below

Accelerator tube window The investigated betatron had an accelerator tube glass window of 1.2 g/cm which implies a root mean square angle of multiple scattering of the electrons in the window as large as 18° at 10 MeV (BETHE & ASHKIN 1960) Scattering foils are, however, needed to adjust the flattening of the beam

Scattering foils The scattering foil in a BBC 35 MeV Asklepitron is profiled in one direction, the one perpendicular to the doughnut plane and of constant thickness in the other direction perpendicular to the beam The maximum thick

ness is between 0 4 and 0 5 mm Cu The present investigation showed that the flattening could be improved if the foils were of elliptic shape and about 3 times thinner than the original ones The shape of the foils were adjusted approximately according to the 70 % isodensity curves measured from photographic films which had been irradiated at the empty foil holder To obtain an optimal flattening the thickness of the foil must be adjusted to the individual thickness of the accelerator tube windows (These vary between about 0 4 to 1 4 g/cm with the BBC 35 MeV Asklepitron) The foil thicknesses given below can only serve as examples

The elliptic foil used at energies up to 29 MeV was made of a uniformly thick 0 1 mm Ag plate the foil used at energies between 30 and 34 MeV comprised three approximately concentric elliptic Cu plates, together giving a maximum thickness of 0 18 mm (0 10 + 0 05 + 0 03 mm Cu) The modified and original foil constructions and the resulting flattenings with these foils are compared in Fig 1

Absorbed dose monitor and collimating system The homogeneity is also influenced by the scattering in the absorbed dose monitor of the BBC betatron and by the method of collimating the beam (Fig 2) The root mean square angle of the electrons scattered in the monitor a transmission chamber (thickness 0 3 g/cm not including an extra balancing chamber see below), is about 5° with 10 MeV electrons More electrons can reach the central than the lateral parts of the treatment fields as a consequence of the large scattering angles and the screening effect of the diaphragm and collimating tube (Fig 2a) This means that the electron fluence rate will be larger on than off the central ray The resulting inhomogeneity cannot be adjusted with scattering foils

SVENSSON & HETTINGER (1967) described a collimating system consisting of a brass field applicator placed close to the skin (Fig 2b) Electrons scattered through large angles in the transmission chamber could also reach points in the treatment fields off the central ray This type of collimating resulted in field sizes with larger homogeneity indices than those obtained with the original perspex tubes The homogeneity was however deteriorated if the patient was not close to the field size applicator a situation occurring now and then in radiation treatment

With a distance between the field size applicator and the patient the homogeneity could be improved if the transmission chamber was taken away from the beam In the present investigation therefore a new absorbed dose monitor system was constructed in order to avoid scattering of the electrons in a transmission chamber (Fig 2c) Two parallel plate ionization chambers one over and one under the doughnut plane were used The position in the electron beam of the new chamber is shown in Fig 3 Both halves of this chamber system are situated outside that part of the beam which reaches the treatment fields

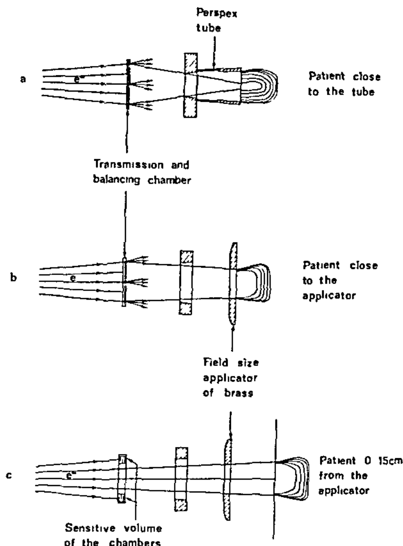


Fig 2 Different beam geometries used with the investigated BBC 35 MeV Asklepitron a) Original transmission monitor chamber extra balancing transmission chamber (PETTERSSON & HETTINGER 1965) and original collimating tubes b) Original transmission monitor chamber extra balancing transmission chamber and field size applicators of brass (SVENSSON & HETTINGER 1967) c) Modified absorbed dose monitor and balancing system and field size applicators of brass (The scattering foils were also modified in this geometry)

Balancing chamber Besides a transmission absorbed dose monitor a large number of BBC betatrons have a balancing chamber in the central part of the beam (PETTERSSON & HETTINGER 1965, VON ARX 1965, ROBINSON & McDOUGALL 1967 and SCHULZ 1969) The purpose of this chamber is to control the flattening in the 'doughnut plane By changing the strength of the extraction field the centre of the electron beam can be shifted from side to side The balancing chamber indicates the best panel setting of the extraction during the

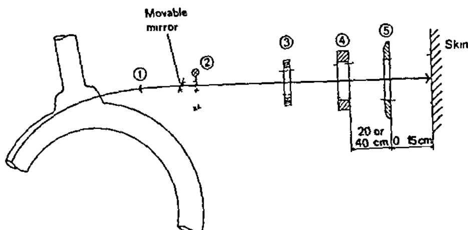


Fig 3 The present beam geometry 1) Modified scattering foil 2) Light field for simulating the radiation field 3) Absorbed dose monitor and balancing chamber outside the central beam 4) Multiple layer diaphragm (BBC original) 5) Collimator plate of brass different field size inserts can be inserted in the plate hole (SVENSSON & HETTINGER 1967)

irradiations. The geometric position of the balancing chamber investigated by the author is hown in Fig 3 The balancing chamber is placed outside that part of the beam which reaches the patient in contrast to the constructions reported earlier

Constructional details of the investigated monitor system and the field size defining system

Monitor system The geometric shapes of the balancing and absorbed dose monitor chambers were made such that they could be placed stationary in the original master collimator of the betatron (Fig 4) The chamber system is divided into four parts A and B are the sensitive volume of the balancing chamber (a section through this chamber is also shown) C and D are the absorbed dose monitor C and D are connected parallel to the electrometer that was used for the original transmission monitor The new absorbed dose monitor has about as large sensitivity as the original one

Field si e defining system The collimator consisted of a multiple layer dia phragm (BBC original) with a hole diameter of 13 5 cm and of a brass plate (Fig 3) The hole in the plate was Φ 14 5 cm used at SSD 101 cm or Φ 17 5 cm used at SSD 121 cm SSD was measured from the enlargement of a crossed wire system according to SVENSSON & HETTINGER (1971) (SSD with the original

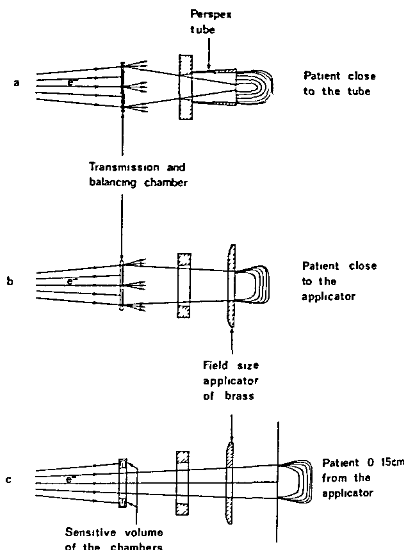


Fig 2 Different beam geometries used with the investigated BBC 35 MeV Asklepitron a) Original transmission monitor chamber extra balancing transmission chamber (PETTERSSON & HETTINGER 1965) and original collimating tubes b) Original transmission monitor chamber extra balancing transmission chamber and field size applicators of brass (SVENSSON & HETTINGER 1967) c) Modified absorbed dose monitor and balancing system and field size applicators of brass (The scattering foils were also modified in this geometry)

Balancing chamber Besides a transmission absorbed dose monitor a large number of BBC betatrons have a balancing chamber in the central part of the beam (PETTERSSON & HETTINGER 1965, VON ARX 1965, ROBINSON & McDOUGALL 1967 and SCHULZ 1969) The purpose of this chamber is to control the flattening in the doughnut plane By changing the strength of the extraction field the centre of the electron beam can be shifted from side to side The balancing chamber indicates the best panel setting of the extraction during the

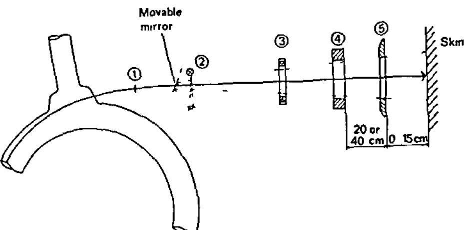


Fig 3 The present beam geometry 1) Modified scattering foil 2) Light field for simulating the radiation field 3) Absorbed dose monitor and balancing chamber outside the central beam 4) Multiple layer diaphragm (BBC original) 5) Collimator plate of brass different field size inserts can be inserted in the plate hole (SVENSSON & HETTINGER 1967)

irradiations. The geometric position of the balancing chamber investigated by the author is shown in Fig 3 The balancing chamber is placed outside that part of the beam which reaches the patient in contrast to the constructions reported earlier

Constructional details of the investigated monitor system and the field size defining system

Monitor system The geometric shapes of the balancing and absorbed dose monitor chambers were made such that they could be placed stationary in the original master collimator of the betatron (Fig 4) The chamber system is divided into four parts A and B are the sensitive volume of the balancing chamber (a section through this chamber is also shown), C and D are the absorbed dose monitor C and D are connected parallel to the electrometer that was used for the original transmission monitor The new absorbed dose monitor has about as large sensitivity as the original one

Field size defining system The collimator consisted of a multiple layer diaphragm (BBC original) with a hole diameter of 13 5 cm and of a brass plate (Fig 3) The hole in the plate was Ø 14 5 cm used at SSD 101 cm or Ø 17 5 cm used at SSD 121 cm SSD was measured from the enlargement of a crossed wire system according to SVENSSON & HETTINGER (1971) (SSD with the original

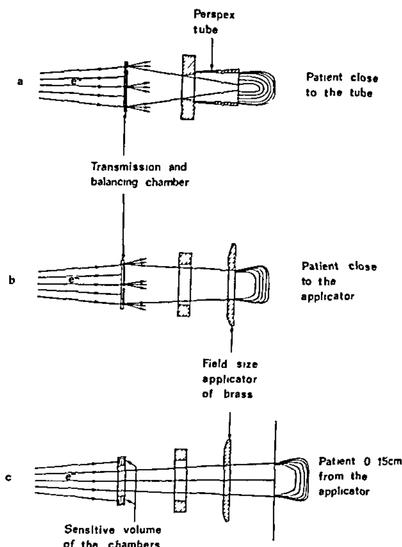


Fig 2 Different beam geometries used with the investigated BBC 35 MeV Asklepitron a) Original transmission monitor chamber extra balancing transmission chamber (PETTERSSON & HETTINGER 1965) and original collimating tubes b) Original transmission monitor chamber extra balancing transmission chamber and field size applicators of brass (SVENSSON & HETTINGER 1967) c) Modified absorbed dose monitor and balancing system and field size applicators of brass (The scattering foils were also modified in this geometry)

Balancing chamber Besides a transmission absorbed dose monitor a large number of BBC betatrons have a balancing chamber in the central part of the beam (PETTERSSON & HETTINGER 1965 VON ARX 1965, ROBINSON & McDOUGALL 1967 and SCHULZ 1969) The purpose of this chamber is to control the flattening in the 'doughnut plane By changing the strength of the extraction field the centre of the electron beam can be shifted from side to side The balancing chamber indicates the best panel setting of the extraction during the

Results and Discussion

Monitor systems The precision of the new absorbed dose monitor has been studied weekly for five months The standard deviation of the monitor calibration factor was 1 % This precision is comparable with the one with the original transmission chamber

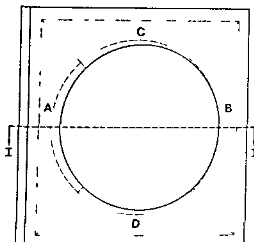
The investigated balancing indicating system has also been checked for a period of five months The checks were carried out once a week with two ionization chambers at 2 cm depth in a polystyrene phantom at SSD 101 cm The measurement points of the chambers were in the doughnut plane 5 cm off the central ray one chamber at each side The measurements showed that the balance of the fields varied with less than 2 % for the whole test period

Definition of the radiation field sizes The matching between the radiation field sizes taken as those defined by the 50 % isodensity curves at 2 cm depths and the light field sizes are better than about 2 mm for the new beam geometry This figure of agreement was valid for energies between 10 and 33 MeV, for field sizes between Φ 4 and Φ 19 cm SSD 101 cm and 121 cm and for distances of 0 to 15 cm between the field size applicator and the patient (Fig 5 B)

Compared with the use of the original foils chambers, and collimating tubes the new system gave the following advantages with respect to the defining of the radiation field sizes (1) the patient set up time is reduced since only the field size inserts have to be changed when another field size is to be used (2) the light field gives better geometric set up accuracy (3) also irregular field sizes can be achieved (4) the maximum field size was increased from about Φ 14 cm with the original system to Φ 19 5 cm with the new one

Homogeneity of the radiation field The homogeneity indices were increased from about 0 6 with the original scattering system to about 0 9 with the new geometry (Fig 5) With the latter geometry the distance from the field size applicator to the patient could be varied from 0 to 15 cm with almost constantly large homogeneity indices The homogeneity indices were only slightly dependent on the incident energy and the field size between Φ 4 and Φ 19 cm

Depth dose curves Depth dose curves measured with the new foils, monitors and collimating system (curves A) are compared in Figs 6 and 7 with curves measured with the original BBC system (curves B) The curves are corrected to infinite SSD with the inverse square law The former geometry involves a smaller amount of material in the electron beam and therefore a smaller energy degradation of the electrons A higher energy about 1 MeV, was therefore set on the instrument panel of the betatron when the latter geometry was used to ensure the same incident energy at the treatment distance (SVENSSON & HETTINGER 1971) The curves A and B differed at depths up to about 2 cm in the sense that the new



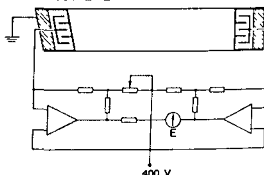
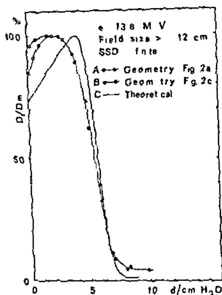


Fig 4 A and B are the sensitive volumes of the balancing chamber a section (I—I) through this chamber is also shown C and D are the sensitive volumes of the absorbed dose monitor The electrodes of the chamber are constructed as in section I—I The chamber is built of aluminium (thicknesses 0 5 and 1 mm) The diameter of the hole is 11 cm E is the balancing indicating instrument (μA meter) on the betatron panel

tubes was determined to 101 cm) The distance between the collimator plate and the patient could be chosen between 0 and 15 cm with good homogeneity (see Results) The maximum field size with SSD 121 cm and a plate — patient distance of 15 cm was ∅ 19 5 cm The collimating plate is supplied with several field inserts defining the field sizes The thickness of the inserts in the beam direction is 18 mm brass

A light field system was constructed to simulate the irradiation field on the patient The lamp intended for simulation of the betatron roentgen ray fields was also used with electron radiation The roentgen and electron beams from the betatron have, however, different directions Two mirrors were therefore used to obtain a suitable light field with the electron beam simulation (Fig 3) The light field has a FSD 3 cm smaller than the SSD with electron radiation This agreement was found to be satisfactory



Fg 6

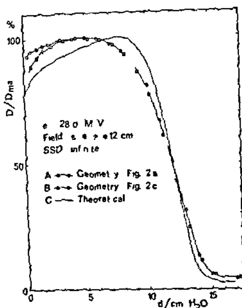


Fig 7

Fg 6 Depth dose cur es at 13 8 MeV Curve A represents the original beam system (fig 2a geometry) B the mod fied beam system (f g 2c geometry) These curves were measured with f rrous sulfat dosimeters Curve C is a theoretical depth dose curv for a parallel monoenergetic electron beam calculat d b BERGER & SELTZER (1969)

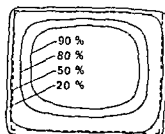
Fig 7 Depth dose curves at 28 MeV Curve A represents the original beam system (fig 2a geometry) B the modified beam system (fig c geometry) These curves were measured with ferrous sulfate dosimeters Curve C is a theoretical depth dose curve for a parallel monoenergetic electron beam calculated by BERGER & SELTZER (1969)

chamber also scatters some electrons out of the treatment field and thus causes a decrease of the absorbed dose rate The new beam geometry meant that the foil thickness was reduced and that the transmission chamber was replaced by a monitor outside the central beam With a mean reduction of the foil thickness of 0 2 mm Cu and with the new monitors the absorbed dose rate was increased at 13 MeV (large field sizes) by about a factor of two The increase was largest at low energies The increase is most important at these energies for radiation treatments The investigated betatron gave with the original foils transmission chamber and collimating tubes a maximum of 30 to 40 rad/min at 13 MeV and about 400 rad/min at 33 MeV (SSD 101 cm and large field sizes)

The collimating tubes also influence the absorbed dose rate SVENSSON & HETTINGER (1967) showed that at 13 MeV with the original tubes and transmission chamber the absorbed dose rate was less than one half with the field size Ø 4 cm

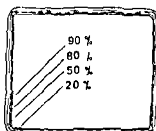
A Original scattering foil monitor and collimating system

B Modified scattering foil monitor and collimating system



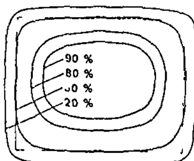
Phantom close to the tube

Homogeneity index 0.65



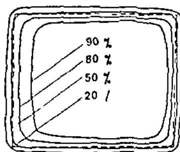
Phantom close to the applicator

Homogeneity index 0.97



Phantom 15 cm from the tube

Homogeneity index 0.51



Phantom 15 cm from the applicator

Homogeneity index 0.88

Fig 5 Results from homogeneity measurements The isodensity curves were measured from films irradiated at 2 cm depth in a polystyrene phantom Curves A are measured with the original BBC beam system (original foil monitor and collimating system) Curves B are measured with the modified system (this latter system is described in figs 2c and 3)

system gave lower relative depth doses The relative depth doses were only slightly different at depths larger than 2 to 3 cm This suggests that the original system gives a somewhat larger contribution of low energy electrons up to about 6 MeV than the new one

Theoretical depth dose curves are also given in Figs 6 and 7 These curves were calculated for a monoenergetic parallel beam incident upon a water phantom (BERGER & SELTZER 1969) The curves in Fig 6 at 13.8 MeV demonstrate that the pure monoenergetic electron beam gives depth dose curves not so suitable for radiation treatment as those from the BBC betatron The plain part has thus almost disappeared in the theoretical monoenergetic curve It also seems with 28 MeV, Fig 7, that further modifications of the beam geometry in order to obtain more monoenergetic electrons does not give a great (if any) improvement of the shape of the depth dose curves for use in radiation treatment

Absorbed dose rate at treatment distance The large cross section for elastic scattering of electrons implies that small increases of the foil thickness give a large decrease of absorbed dose rate at treatment distance The transmission

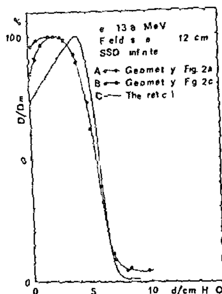


Fig 6

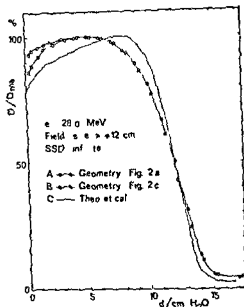


Fig 7

Fig 6 Depth dose *curves at 13 8 MeV* Curve A represents th original beam system (fig 2a geometry) B the modified beam system (fig 2c geometry) These curves were measured with ferrous sulfate dos m ters *Curve C is a theoretical* depth dose curve for a parallel mono-energetic electron beam calculated by BERGER & SELTZER (1969)

Fig 7 Depth dose curves at *28 MeV* Curve A represents the original beam system (fig 2a geometry) B the modified beam system (fig 2c geometry) These curves were measured with ferrous sulfate dos meters Curve C *is a theoretical* depth dose curve for a parallel mono-energetic electron beam calculated by BERGER & SELTZER (1969)

chamber also scatters some electrons out of the treatment field and thus causes a decrease of the absorbed dose rate The new beam geometry meant that the foil thickness was reduced and that the transmission chamber was replaced by a monitor outside the central beam With a mean reduction of the foil thickness of 0 2 mm Cu and with the new monitors the absorbed dose rate was increased at 13 MeV (large field sizes) by about a factor of two The increase was largest at low energies The increase is *most important* at these energies for radiation treatments The investigated betatron gave with the original foils transmission chamber and collimating tubes a maximum of 30 to 40 rad/min at 13 MeV and about 400 rad/min at 33 MeV (SSD 101 cm and large field sizes)

The collimating tubes also influence the absorbed dose rate SVENSSON & HETTINGER (1967) showed that at 13 MeV with the original tubes and transmission chamber the absorbed dose rate was less than one half with the field size ϕ 4 cm

than with ϕ 12 cm The difference depended on the fact that with large field size more electrons, which had an angle direction different from the central ray, reached the treatment field These electrons were, however, screened from the treatment field, when small collimating tubes were used The deflection of the electrons occurred mainly in the transmission chamber

With the new geometry, without transmission chambers and collimating tubes the absorbed dose rate was almost the same with small and large field sizes The total increase of the maximum absorbed dose rate with the new system compared with the original one was therefore dependent both on the electron energy and on the field size The increase was, for example equal to a factor of 2 to 4 at 13 MeV for field sizes between ϕ 12 and ϕ 4 cm

Acknowledgement

The author gratefully acknowledges technical suggestions of Mr B Sjostrom This work was supported by grants from the Swedish Cancer Society

SUMMARY

The *scattering geometry of the electron beams* with a Brown Boveri 35 MeV Asklepitron was studied The experiments led to modifications of scattering foils transmission and balancing ionization chambers and of the collimating system It was possible to improve the flattening of the treatment fields to decrease the relative depth doses at small phantom depths to increase the absorbed dose rate and the maximum field sizes Furthermore a better patient set up accuracy was achieved as the field sizes are simulated by a light field on the patient

ZUSAMMENFASSUNG

Es wurde die Streu Geometrie der Elektronenstrahlen eines Brown Boveri 35 MeV Asklepitron untersucht Die Untersuchungen fuhrten dazu dass die Streufolien die Transmissions und Ausgleichs Ionisations kammern und das Kollimatorsystem verandert wurden Es war moglich die Abflachung des Behandlungsfeldes zu verbessern die relativen Tiefendosen bei geringen Phantomtiefen herabzusetzen die absorbierte Dosisleistung und die maximalen Feldgrossen zu erhohen Ausserdem wurde eine hohere Genauigkeit der Patient einstellung dadurch erreicht dass die Feldgrossen durch ein Lichtfeld auf dem Patienten *dargestellt* wurden

RÉSUMÉ

L auteur a etudie la geometrie de la dispersion des faisceaux d electrons avec un Asklepitron de 35 MeV de Brown Boveri Les experiences ont conduit a modifier les ecrans de *dispersion* la transmission et l equilibrage des chambres d ionisation et le systeme de colli

mation Ceci a permis d'améliorer la planéité des champs de traitement de diminuer les doses en profondeur relative pour des profondeurs de petit fantome d'augmenter le taux de dose absorbée et les dimensions maximales des champs De plus on a obtenu une mise en place plus précise du malade étant donne que les dimensions de champ sont simulées par un champ lumineux sur le malade

REFERENCES

VON ARX A Continuous or periodical control of field homogeneity *In* Symposium on high energy electrons p 85 Edited by A Zuppinger and G Poretti Springer Verlag Berlin 1965

BERGER M J and SELTZER S M Quality of radiation in a water medium irradiated with high-energy electron beams Paper presented at the 12th International Congress of Radiology Tokyo Japan October 1969

BETHE H A and ASHKIN J Passage of radiations through matter Section 2 Penetration of beta rays through matter *In* Experimental nuclear physics Vol I p 252 Edited by E Segre John Wiley and Sons New York 1960

PETTERSSON C. and HETTINGER G A balancing chamber for stabilizing the homogeneity of the electron field between 10 and 35 MeV *In* Symposium on high-energy electrons p 89 Edited by A. Zuppinger and G Poretti Springer Verlag Berlin 1965

ROBINSON J E and MCDOUGALL R S Electron beam instability and isodose asymmetry associated with a 35 MeV medical betatron Phys in Med Biol 12 (1967) 315

SCHULZ R J Problems of inhomogeneous media and beam shaping with high energy electrons *In* Symposium on high-energy electrons p 133 Edited by C Gil y Gil and Gil C Gayarre General Directorate of Health Madrid 1969

SVENSSON H and HETTINGER G Influence of collimating systems on dose distribution from 10 to 35 MeV electron radiation Acta radiol Ther Phys Biol 6 (1967) 404

— — Dosimetric measurements at the Nordic medical accelerators I Characteristics of the radiation beam Acta radiol Ther Phys Biol 10 (1971) 000

FROM THE DEPARTMENTS OF RADIATION PHYSICS (DIRECTOR ASSOC PROF H SKOLDBORN) AND RADIOTHERAPY (DIRECTOR PROF M STRANDQVIST), SAHLGRENSKA SJUKHUSET, UNIVERSITY OF GOTHENBURG, SWEDEN

COLLIMATING SYSTEM FOR ELECTRON BEAMS

by

BENGT LINDSKOUG and ARNE DAHLER

Electron beams are usually defined by collimators consisting of a diaphragm and a cone *Materials for collimation have been examined at several laboratories* (BEATTIE et coll 1962, LOEVINGER et coll 1961, SEMPERT 1960, LAUGHLIN et coll 1953) The cone walls are made of low atomic weight materials such as lucite, aluminium duralumin or brass, of these lucite possesses the advantage of being transparent The wall material increases the dose rate due to the increased content of scattered electrons, these contribute to the skin dose and to the superficial part of the central axis depth dose (LOEVINGER et coll 1961, BRADSHAW & MAYSENT 1964)

Collimation of electrons for radiation therapy involves physical as well as *practical problems Shielding palpation and tatooing in the region treated are* difficult when closed applicators are used, in the head and neck regions the cones *often fail to make good contact with the skin Physically it is dose* rate, homogeneity skin dose and the dose distribution at the edges of the field that are influenced by the collimating system

Improvements in the standard cones have been reported DAHLER (1964) described a straight lucite tube furnished with a thin layer of metal at the edges

Submitted for publication *26 October 1970*

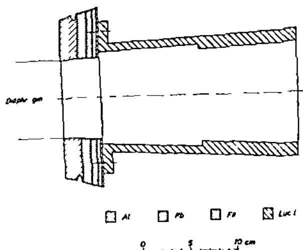


Fig 1 The BBC standard collimator

to give a better dose distribution SVENSSON & HETTINGER (1967) met most of the physical requirements with brass plates defining the field size they reported that the dose rate increased considerably with a wider aperture in the betatron

The following work was done on a Brown Boveri Corp (BBC) betatron Asklepitron 35

A standard collimator (Fig 1) is inserted into a metal box, called the master collimator containing the monitor chamber The sandwich consisting of 18 mm Al 10 mm Fe, 5 mm Pb and 5 mm Fe and the lucite walls converge to a point 110 cm from the edge of the cone The scattering contribution to the surface may be determined by exposures perpendicular to the beam direction with the films on the surface of the phantom and at the depth of the maximum dose The relative densities produced in three exposures of six films in this way in a polystyrene phantom appear in Fig 2 (100 per cent at maximum dose) Sandwich plus cone sandwich alone and metal frame (3 5 mm Al + 0 5 mm Pb) were used The metal frame placed in contact with the phantom defined the same field size as the cone but with the maximum aperture in the sandwich The first two exposures (curve a) have equal density distributions across the beam but the surface density is higher with the cone The essential collimation is accomplished by the sandwich The metal frame increases the surface density even more (curve b) but at the depth of maximum dose the beam is well defined by the improved distribution at the margins

The present design was prompted by experiences with a metal frame defining the field size close to the patient (SVENSSON et coll 1967) However, the collimation ought to be more easily adapted to the body contours

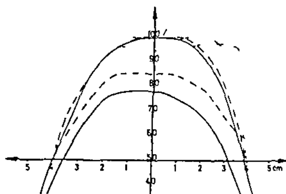


Fig 2 Relative density of films irradiated at the surface and at depth of maximum dose (100 per cent) for a) original collimating system with (— —) and without (—) lucite cone b) metal frame collimator ( ) with the same opening 8 cm ⌀

The possibilities of palpation in the field as well as tatooing the field were agreed by the clinicians as being desirable The effect of improving the do e rate by increasing the aperture has been reported elsewhere (LINDSKOUG & JOHANSSON 1971)

Thirty MeV electrons were used in the determination of transmission and activation Plates of different materials were placed in front of a polystyrene phantom (20 cm × 20 cm × 30 cm) and irradiated perpendicularly, an ionization chamber of transmission type (LINDSKOUG 1966) was placed at a depth of 3 cm in the phantom Fig 3 indicates the relative ion currents against thickness of Al, *Pb* and lucite, the transmission through *Pb* and *Al* equalling that reported by LOEVINGER et coll (1961) The minimum of bremsstrahlung, mass and geometric extension was the object of the experiment The most interesting part of the diagram is enlarged in Fig 4, where some plate combinations are al o presented The combination of 10 mm DAl + 5 mm Fe + 5 mm Pb, was chosen due to its small mass and geometric extension It permits 8 5 per cent transmission

A sensitive radiation protection instrument (Jordan, Model AGB 10KG SR) was used to obtain the relative induced activities in some of the materials of interest The plates were irradiated with 400 rad The activation is due to (γ, n) reactions from the generated bremsstrahlung The Jordan instrument was placed in a test jig, 65 mm from the irradiated metal plate (see Figs 5, 6) and the instrument reading was recorded at predetermined intervals, the recording for brass was taken as 100 per cent Al and Fe produce small activities that soon decay The activity of brass has two components ^{62}Cu ($T_{1/2}$ = 10 15 min) and ^{63}Zn ($T_{1/2}$ = 38 3 min) Brass is the material that gives highest activity After a second irradiation this time with 5 000 rad the brass plate was found still to have a measurable activity 930 minutes (15 5 h) after irradiation (Fig 6)

Cumulation of activity appears to be a definite risk only if a collimator of brass be used frequently

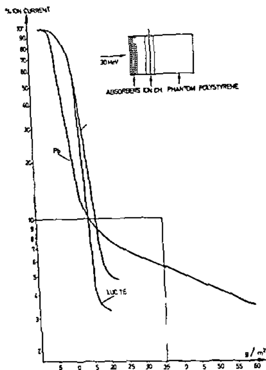


Fig 3 Relative ionization current against surface thickness of Al Pb and lucite

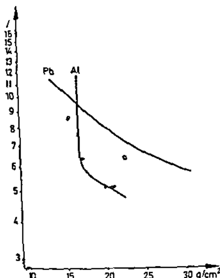


Fig 4 Relative ionization current against surface thickness of Al Pb and some combinations of metal plates

o Al + Pb □ Al + Fe + Pb × duralumin + steel ● duralumin + Pb + duralumin + steel + Pb

Table 1

Collimators and corresponding insets (dimensions in cm)

Collimator	Insets
14 × 14	14 × 10 14 × 8 12 × 12
10 × 10	10 × 8 10 × 6 8 × 8 6 × 6
O 14	O 12
O 10	O 8
O 6	—

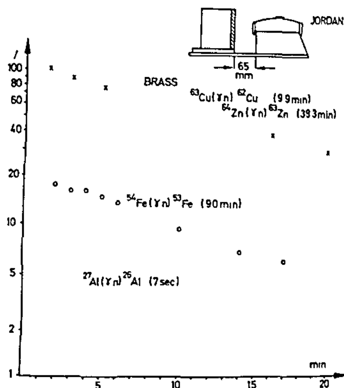


Fig. 5. Set up and the induced activity in Al, Fe and brass after irradiation (400 rad, 0.35 mR/h) with 30 MeV electrons (t = 0 at end of irradiation)

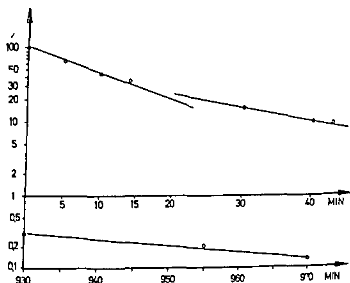


Fig. 6. Induced activity in brass irradiated with 5 000 rad (6.2 mR/h, t = 0 at 5 min after irradiation)

A set of collimators was made with several insets defining the field size as listed in Table 1. The design was as follows. A 2 cm broad frame composed of the chosen metal sandwich and defining the field was made. The leading 30 mm consisted of a 50 mm lucite extension, 5 mm thick, which could be changed

Table 2

Skin dose as percentage of dose at maximum depth

Energy MeV	10	15	20	25	30	[illegible]
Skin dose	91	88	[illegible]	94	92	[illegible]

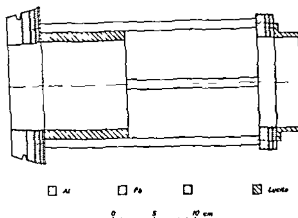


Fig 7 The new collimator construction for a 10 cm × 10 cm field

easily and machined to fit irregular surfaces furthermore the lucite extension would separate the skin and the metal frame a factor of importance as the frame edge is the source of scattered electrons contributing to the surface dose Experiments on glancing angle electron scatter have indicated the presence of small angle scattering and independently of wide angle scattering (LOEVINGER et coll 1961)

The collimator defining the field size 10 cm × 10 cm is schematically depicted in Fig 7 Fifteen and 30 MeV ionodose diagrams are collected for comparison with the corresponding diagrams for the standard lucite collimator (Fig 9) The collimator defining the field size 14 cm × 14 cm is represented with different insets in Fig 8

The density distribution outside the metallic frame in a film exposed at right angles to the beam is depicted in Fig 10 The density is approximately 17 per cent of that measured within the beam This effect was due to wide side scattering from the diaphragm and was eliminated by mounting a lucite screen just in front of the sandwich A suitable length was experimentally found to be 100 mm the density decreased to 4 3 per cent The dose distribution on the surface inside and outside the radiation field was determined by thermoluminescence dosemeters

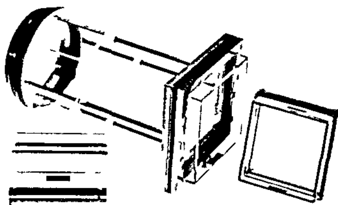
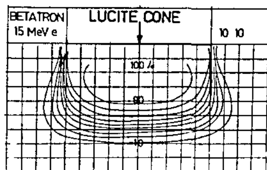
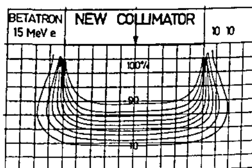
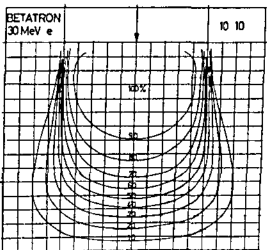


Fig 8 Collimator field size 14 cm × 14 cm with two different insets







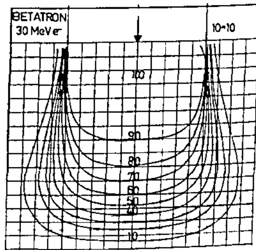


Fig 9 Comparison of isodose diagrams with a lucite cone and the new collimating system with energies of 15 and 30 MeV field size 10 cm × 10 cm

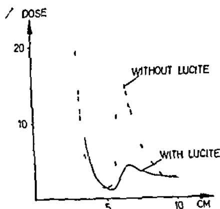


Fig 10 Edge effect investigations

(extruded LiF rods Harshaw) The e were placed at the surface of a lucite plate with grooves to fit the rods and the absolute and the relative doses at the surface and at the maximum do e were determined contamination of scattered low energetic electrons outside as well as inside the frame were evident Representa tive kin dose values are given in Table 2 The surface dose measurements were confirmed by films and the agreement with the LiF was within ± 2 per cen The standard error for these measurements were kept within ± 2 per cent by individual calibration and track of the LiF do emeters

A brief investigation concerning the use of paraffin as blocking material in electron beams has been given by DAHLER (1968) He concluded that lead is far superior to paraffin and other equivalent materials in this respect special protective devices of lead have been designed to be attached to the collimator frames

An urethra protection block 12 mm ∅ and 5 mm thick was designed for use in the treatment of carcinoma of the vulva so as to be conveniently arranged in the field (Fig 11 a) The corresponding isodensity distribution in a film ex posed perpendicular to the beam appears in Fig 11 b The film was measured with a semi automatic isodensity recorder system (SKOLDBORN 1966)

The new collimators have the following advantages in comparison with tho e of the standard type (lucite tubes) (1) higher dose rate (2) better do e gradient at the edges of the beam (3) easier set up with the possibility of marking and palpating in the field (4) they can be machined to fit various body contours (5) the field sizes are easily changed by insets and (6) beam shaping blocks may easily be attached The collimators have been used routinely for one year No problems have arisen during this time and the clinicians and

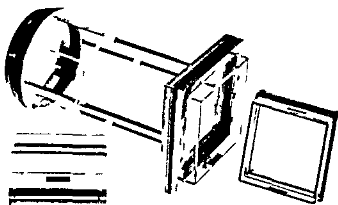
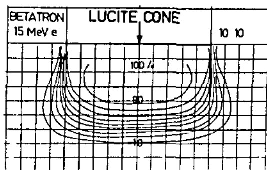
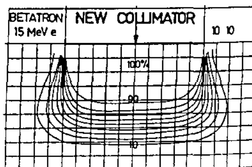
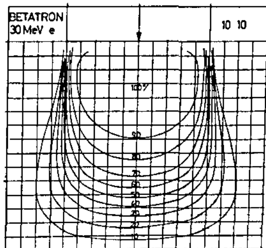


Fig 8 Collimator field size 14 cm × 14 cm with two different insets







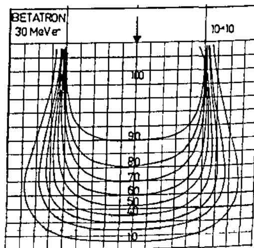


Fig 9 Comparison of isodose diagrams with a lucite cone and the new collimating system with energies of 15 and 30 MeV field size 10 cm × 10 cm

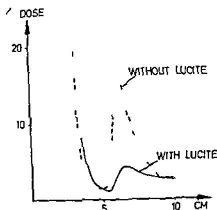


Fig 10 Edge effect investigations

(extruded LiF rods Harshaw) These were placed at the surface of a lucite plate with grooves to fit the rods and the absolute and the relative doses at the surface and at the maximum dose were determined contamination of scattered low energetic electrons outside as well as inside the frame were evident Representative skin dose values are given in Table 2 The surface dose measurements were confirmed by films and the agreement with the LiF was within ± 2 per cen The standard error for these measurements were kept within ± 2 per cent by individual calibration and track of the LiF dosemeters

A brief investigation concerning the use of paraffin as blocking material in electron beams has been given by DAHLER (1968) He concluded that lead is far superior to paraffin and other equivalent materials in this respect special protective devices of lead have been designed to be attached to the collimator frames

An urethra protection block 12 mm ∅ and 5 mm thick was designed for use in the treatment of carcinoma of the vulva so as to be conveniently arranged in the field (Fig 11 a) The corresponding isodensity distribution in a film exposed perpendicular to the beam appears in Fig 11 b The film was measured with a semi automatic isodensity recorder system (SKOLDBORN 1966)

The new collimators have the following advantages in comparison with those of the standard type (lucite tubes) (1) higher dose rate (2) better dose gradient at the edges of the beam (3) easier set up with the possibility of marking and palpating in the field (4) they can be machined to fit various body contours (5) the field sizes are easily changed by inserts and, (6) beam shaping blocks may easily be attached The collimators have been used routinely for one year No problems have arisen during this time and the clinicians and

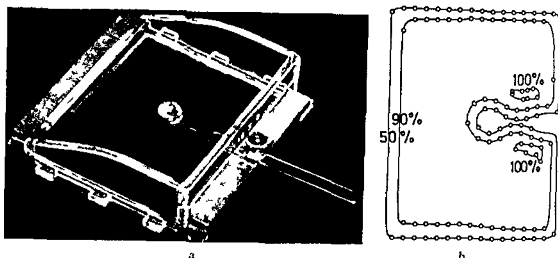


Fig 11 a) Protecting device for the urethra b) Accompanying field distribution at depth of maximum dose Energy 20 MeV

the radiotherapy assistants working with them find them practical and easy to handle

Acknowledgements

The authors are indebted to Prof Holger Skoldborn and Mrs Inger Ragnhult for stimulating criticism during this work They gratefully acknowledge the cooperation and assistance of Messrs K A Johansson B T Bengtsson and Mrs B Feltzing in the measurements Special thanks are due to Messrs R Kellgren and A Kristensson for advice in the contruction stage and for the final engineering of the collimators Mrs B Ohlson drew all the diagrams and Mr O Roos was responsible for the photographic reproduction

SUMMARY

A new collimating system for electron beams with which extensive measurements including those of induced activity skin dose and scatter conditions have been performed is described This appears to constitute a general improvement on the standard cones as regards dose distribution and dose rate achieved by means of a field defining diaphragm of a special sandwich type

ZUSAMMENFASSUNG

Ein neues Einblendungssystem fur Elektronenstrahlenbundel wird beschrieben Umfassende Messungen mit Einschluss solcher der Sekundarstrahlung der Hautdosis und der Streustrahlung wurden vorgenommen Es zeigte sich dass die neue Blende dem bisher gebrauchlichen Tubus hinsichtlich Dosenfluss und Dosenverteilung uberlegen ist Dieses Resultat wird durch eine besser konstruierte Blende die aus mehreren Schichten besteht erreicht

RÉSUMÉ

Les auteurs decrivent un nouveau systeme de collimation pour les faisceaux d electrons qui a permis des mesures variées y compris la mesure de l activité induite de la do e à la peau et des conditions de dispersion Ce collimateur parait constituer un perfectionnement general par rapport aux cones standards en ce qui concerne la distribution de dose et le debit de dose obtenu au moyen d un diaphragme delimitant le champ d un type special en sandwich

REFERENCES

BEATTIE J W TSIEN K C OVADIA J and LAUGHLIN J S Production and properties of hi h energy electrons for therapy Amer J Roentgenol 88 (1962) 235

BRADSHAW A L and MAYSENT A M Physical aspects of electron therapy using the 15 MeV linear accelerator Brit J Radiol 37 (1964) 219

DAHLER A Effect of collimator shape on electron depth dose curve *In* Proceedings of the international symposium on high energy electron Montreux p 98 Springer Verlag Berlin 1964

— Blocking of fields in electron beam therapy *In* Proceedings of the Fifth Nordic Meeting on Clinical Physics Saltsjobaden Sweden 1968

LAUGHLIN J S OVADIA J BEATTIE J W et coll Some physical aspects of electron beam therapy Radiology 60 (1953) 165

LINDSKOUG B och JOHANSSON K A Inmatning av 35 MeV betatronen vid Sahlgrenska sjukhuset i Goteborg (In Swedish) *In* Proceedings of the Fourth Nordic Meeting on Clinical Phys cs Hanko Finland (1966) 72

— — Collimator and scattering foil for 10—20 MeV electrons Acta radiol Ther Phys Biol 10 (1971) 21

LOEVINGER R KARZMARK C J and WEISBLUTH M Radiation therapy with high energy electrons Radiology 77 (1961) 906

SEMPERT M New developments in high energy electron beam therapy with the 35 MeV Brown Boveri Betatron Radiology 74 (1960) 105

SKOLDBORN H En ny semiautomatisk isosvartningsskrivare (In Swedish) *In* Proceedings of the Fourth Nordic Meeting on Clinical Physcis Hanko Finland (1966) 67

SVENSSON H and HETTINGER G Influence of collimating systems on dose distribution from 10 to 35 MeV electron radiation Acta radiol Ther Phys Biol 6 (1967) 404

Book review

APPLIED RADIATION PROTECTION AND CONTROL By J J Fitzgerald 1018 pages 353 figures and 156 tables Gordon and Breach, New York London and Paris 1970 Price $30

The emphasis of this monograph is on the needs of nuclear energy work The book abounds with tables diagrams and formulae and will certainly be extremely useful to all those engaged in designing protective shields and other devices assessing criticality hazards and planning radiation laboratories as well as supervising work in them It should be added however that the book is based on an earlier one by the author and two collaborators on the mathematical theory of radiation dosimetry There are numerous references to the earlier work which should be constantly at hand if full benefit is to be reaped from the present material

The subject matter seems to be well covered, although the more recent literature sometimes appears to be ignored It is for instance remarkable that the ICRP recommendations are quoted (pp 22—23) from a paper of 1960 Repetition in different parts of the book makes it bulkier that it need have been

Little is said about roentgen ray protection and most radiologists will not require the book As a collection of data and formulae relating to the dosimetry of external and internal radiation it will however be of value to physicists engaged in dosimetric and radiation protection questions and to specialists in nuclear medicine

Sven Benner

ACTA RADIOLOGICA

OFFICIAL ORGAN OF THE RADIOLOGICAL SOCIETIES OF
DENMARK FINLAND NORWAY AND SWEDEN

Vol 10 Fasc 5 | THERAPY PHYSICS BIOLOGY | 1971 October

CARCINOMA OF THE HYPOPHARYNX

Therapeutic results in a series of 103 patients

by

KARSTEN JØRGENSEN

The review covers 103 of a total of 108 patients with carcinoma of the hypopharynx admitted during the 25 year period 1944—1969 The 5 patients excluded comprised 3 who had had treatment elsewhere and 2 in whom the histologic diagnosis was uncertain The distribution of the patients into five year periods appears in Table 1 The material consisted of 62 men (60 per cent) and 41 women (40 per cent) aged as in Fig 1 All the lesions consisted of squamous-cell carcinoma

The primary manifestations distributed by percentage were

Dysphagia	46 % (48/103)
Soreness pain or irritation	30 % (31/103)
Hoarseness	9 % (9/103)
Lump in the neck	9 % (9/103)

The remaining patients were distributed as follows

Cough	3 patients
Weight loss	2 patients
Ear pain	1 patient

From the Radium Centre (Director Sigvard Kaae) and the E N T Department (Director H C Andersen) Municipal Hospital of the University of Århus Denmark Submitted for publication 1 February 1971

Table 1

A total of 103 patients with carcinoma of the hypopharynx subdivided into 5 year periods

	No of patients
1944—49	19
1949—54	18
1954—59	21
1959—64	19
1964—69	26
Total	103

The diagnosis was made within four months of the onset of the symptoms in 63 (61 %) of the patients

The pyriform sinus was affected in nearly half the material About 53 % of patients had cervical lymph node metastases when admitted and 6 % distant metastases, the frequency of nodal metastases was highest in the pyriform sinus group, or 30/50 (60 %)

The lower part of the hypopharynx, which lies at the posterior aspect of the cricoid cartilage and at the posterior pharyngeal wall, is of particular interest A total of 53 patients, 28 or 53 % women, were affected in this region (cf Table 2) The case notes were carefully searched for any history of dysphagia Seventeen of the 53 patients had had dysphagia from 1 to 40 years before the diagnosis and, when accurately described, apparently consisted of a feeling of postcricoid obstruction and delayed swallowing Dysphagia occurred in 20 patients, 18 of whom were women The growth in 17 was situated in the lower part of the hypopharynx and in the pyriform sinus in 3 patients The total thus contains a group characterized by (1) a long history of dysphagia (2) female sex, and (3) a lesion in the lower part of the hypopharynx

No analysis was made of nail changes, rhagades at the corners of the mouth, atrophic mucosal changes, and glossitis, as the data on these signs were incomplete Membrane formation was evident in the oesophageal opening by oesophagoscopy in 2 patients after the tumour had disappeared

The review of the case notes suggested other possible predisposing factors Two patients had suffered from pernicious anaemia for seven and ten years and 4, including 2 patients with rheumatoid arthritis had had chronic anaemia Two of these 6 patients developed carcinoma of the pyriform sinus and 4 patients of the lower part of the hypopharynx

Method of treatment All patients treated first received irradiation Treatment

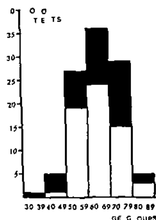


Fig 1 Age distribution at the time of the histologic diagnosis black fields indicating women and the white columns those of men in the series

was withheld in 3 patients because of advanced age and a poor general condition Eighty seven patients had radiation doses within the cancerocidal range with a tumour dose of about 6 000 R over 6 weeks Thirteen received lower doses

Palliative irradiation (3 000—5 000 rad)	6 patients
Treatment abandoned after a few sessions	6 patients
Died early in treatment	1 patient

The irradiation up to 1963 was delivered by a conventional unit and then by a ^{60}Co unit of kilocurie strength The therapeutic method as well as the follow up were practically identical with those employed for carcinoma of the larynx and already described in detail (JØRGENSEN 1970, JØRGENSEN & SELL 1971)

Results

Eighty seven patients received curative irradiation 16 out of 69 of whom with residual tumours or recurrence underwent operation The nature and number of the operations are listed below

	No of patients
Partial pharyngectomy and neck dissection	2
Total laryngectomy and partial pharyngectomy	6
Total laryngectomy and partial pharyngectomy and neck dissection	3
Total laryngectomy and total pharyngectomy and neck dissection	2
Neck dissection alone	3
Total	16

Table 2

TNM classification of 103 patients with carcinoma of the hypopharynx during the period 1944—1969

		N0	N1	N2	N3	Total
Pyriform sinus	T1	3	2	1	2	50 (49 %)
	T2	7	1	3	1 (1M1)	
	T3	10	9	2	9 (3M1)	
Postericoid	T1	5	1	—	2 (1M1)	30 (29 %)
	T2	3	1	—	3	
	T3	9	4 (1M1)	—	2	
Posterior wall of pharynx	T1	4	2	—	3	23 (22 %)
	T2	5	1	—	—	
	T3	2	1	1	4	
Total	T1	12	5	1	7	
	T2	15	3	3	4	
	T3	21	14	3	15	
		48	22	7	26	

Four of the 16 patients have died from other causes without recurrence 1, 3, 4 and 11 years after treatment and 3 are alive and well at 1 1/2, 4 1/2 and 7 years. The operative procedures included two total pharyngectomies ad modum Wookey with reconstruction of the pharynx by means of duplicated skin flaps. One of these patients has managed very well for 11 years, while the other died of a recurrence a few months after the operation.

The survival curve for all 103 patients is given in Fig. 2 and thus includes both treated and untreated patients. The curve represents the results of calculating the mortality coefficients for the individual years of the follow up period (NOHRMAN 1953, JORGENSEN & SELL 1971). As the analysis extends to 1 January 1969 the control periods of 4 of 8 survivors are short. In accordance with the method of calculation, these 4 patients still alive were withdrawn at the following times: 2 patients in the 2nd and 3rd year of follow up and 2 patients in the 5th year. The standard error on the expected 5 year result is 3.5 % and × 2 the standard error 7.0 % is plotted (Fig. 2). The 5 year crude survival is thus 16 ± 7 %.

Correction was made for mortality from causes other than carcinoma of the hypopharynx: the survival curve corrected for mortality from such causes is plotted in Fig. 2. The 5 year result is 23 %, i.e. three quarters of the patients

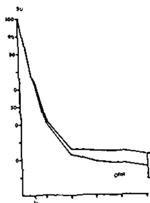


Fig 2



Fig 3

Fig 2 Survival curves for 103 patients with carcinoma of the hypopharynx The upper curve is corrected for mortality from causes other than carcinoma the lower curve is uncorrected

Fig 3 Survival curves for 32 patients with carcinoma of the hypopharynx treated by a ^{60}Co kilocurie unit during the period 1963—1969

succumb to hypopharyngeal carcinoma The survival curve is an almost direct expression of the therapeutic result as only 3 patients had no form of treatment A survival curve representing the treated patients would be slightly higher and the 5 year result would be 17 % crude survival

The therapeutic results for the group of patients who had irradiation and who have been followed for more than 5 years are interesting A total of 74 had irradiation during the period up to 1 January 1965 Seven were subjected to operation for residual tumours or recurrences (Table 3) The crude 5 year survival rate for these 74 patients was 19 % (14/74) corrected for deaths from causes other than carcinoma the 5 year survival becomes 27 %

The relation between the prognosis and the stage of the disease on diagnosis was assessed on the basis of all patients having a control period exceeding 5 years a total of 86 patients (Table 4) Fig 2 gives the results for the entire 25 year period As mentioned above high voltage treatment was introduced in early 1963 and up to 1 January 1969 a total of 32 patients had thus been treated The survival curve for these patients is on an improved although not significantly better level (Fig 3)

Side effects of irradiation and of surgery Severe reactions to the radiation therapy occurred in 11 patients and in 6 the irradiation was discontinued for this reason Two patients required tracheotomy during the treatment Trouble

Table 3

Results of treatment of 74 patients with carcinoma of the hypopharynx observed for more than 5 years

No of patients	5 year survival		Crude 5 year survival rate
	Irradiation alone	IRR+Surg for recurrences and res *	
74	12/74	2/74	14/74 (19 %)

* IRR = irradiation Surg = surgery after failure of irradiation res = residual tumour

Table 4

Relation between prognosis and stage of disease

	No of patients	Crude 5 year survival rates
T1N0M0 / T2N0M0	24	6/24 (25 %)
T3N0M0	17	2/17 (12 %)
T1+2+3 / N1+2+3	45	4/45 (9 %)

some sequelae also occurred later Thus more than a third of the patients who survived for over 2 years had persistent, major pharyngeal complaints, consisting in dryness and irritation of the throat and sometimes dysphagia

The operations carried no immediate mortality, but one patient died from erosion of the carotid artery 33 days later Four patients developed temporary fistulae to the pharynx, one had to be treated surgically, while the others closed spontaneously Partial pharyngectomy never gave rise to serious disturbances in swallowing

Discussion

The TNM classification in the UICC modification (1968) was used in the analysis of the series of 103 patients from a 25 year period Owing to the special anatomic conditions, it was difficult to classify major tumours accurately, so that the grouping carries some inaccuracy Similar experience has been reported by LILLIS (1968) as well as by McCREA & DICKIE (1968)

Carcinoma close to the oesophageal opening is more common in women than in men This is remarkable since at all other sites in the upper digestive tract it occurs more often in men (CLEMMESEN 1965), this was confirmed in the present material

Plummer Vinson sideropenic dysphagia is generally considered a precancerous state This assumption is supported by the present findings as at least 33 % (17/53) of the patients with carcinoma of the lower part of the hypopharynx probably had this syndrome Similar findings have been reported from Sweden where AHLBOM (1936) and later WYNDER et coll (1957) reported that 70 % of patients with hypopharyngeal carcinoma were affected in a large British eries JONES (1961) gave a figure of 30 %

The survival figures are on the ame low level as given by SMITH et coll (1963) DALLEY (1968) and McCREA & DICKIE (1968) (Figs 2 3) The introduction of high voltage irradiation does not appear to have been revolu tionary although ome improvement may have occurred (Fig 3)

Relatively few patients could for several reasons have secondary operation removal of malignant remnant or recurrence was often out of the question because of the patient s poor general condition or not infrequently because it was impossible

As already mentioned the therapeutic schedule throughout the period has always been primary irradiation with a curative aim and possible secondary operation if possible It must be mentioned that planned combined therapy with a radiation dose of 5 500 R and operation three weeks later has afforded promising results elsewhere (GOLDMAN et coll 1968 1969 OGURA & BILLER 1970) BILLER et coll (1969) analysing cases of carcinoma affecting the pyriform sinus and vallecula reported that even low doses of preoperative irradiation (1 500—3 000 R) significantly reduced the recurrence rate Their material was however of limited size and was not TNM classified All considered then it must be said that o far procedures different from that now reported have *not* given better results the materials mentioned having been of limited ize or with short follow up periods

SUMMARY

A *series of 103* patients with carcinoma of the hypopharynx from the period 1944—1969 was analysed The 5 year crude survival rate for the entire material was 16 per cent Thirty two patients received primary ^{60}*Co irradiation* during the period 1963—1969 the 5 year survival rate for this group being calculated as 22 per cent the result corrected for death from other causes is expected to be 34 per cent Cure is effected by primary ^{60}Co irradiation sometimes supplemented by surgery in 33 per cent of patients

ZUSAMMENFASSUNG

Es wurde eine Serie von 103 Patienten der Periode 1944—1969 mit einem Carcinom des Hypopharynx analysiert Die 5 Jahres Überlebensrate des gesamten Materials betrug 16 Prozent Von 32 Patienten, die während der Periode 1963—1969 primar ^{60}Co Bestrahlun erhalten hatten betrug die 5 Jahres Überlebensrate 22 Prozent wird dieses Resultat fur *Todesfalle infolge* anderer Ursachen korrigiert ist mit 34 Prozent zu rechnen Bei primarer Bestrahlung mit ^{60}Co gelegentlich chirurgisch komplettiert kann in 33 Prozent der Patienten Heilung erzielt werden

RÉSUMÉ

L auteur analyse une serie de 103 malades atteints de cancer de l hypopharynx au cours *de la periode 1944—1969 Le taux brut de survie a 5 ans pour l ensemble de la serie a ete* de 16 pour cent Trent deux malades ont reçu une irradiation primaire par ^{60}Co au cours de la periode 1963—1969 le taux de survie a 5 ans pour ce groupe a ete de 22 pour cent le *resultat corrige pour tenir compte des deces d autres causes est estime a 34 pour cent* Le traitement est fait par irradiation primaire par ^{60}Co quelquefois complete par la chirurgie chez 33 pour cent des malades

REFERENCES

AHLBOM H E Om anami och dysphagi Plummer Vinson s syndrom i sjukhistorien hos kvinnor med cancer i mun svalg och matstrupe (In Swedish) Nord T mod Sjukhus 1 (1936) 171

BILLER H F OGURA J H DAVIS W H and POWERS W E Planned pre operative irradiation for carcinoma of the larynx and laryngopharynx treated by total and partial laryngectomy Laryngoscope 79 (1969) 1387

CLEMMESEN J Statistical studies in the aetiology of malignant neoplasms Acta path micro biol scand Suppl No 174 (1965) Part 2

DALLEY V M Cancer of laryngopharynx J Laryng 82 (1968) 407

ELLIS M Cancer of the laryngopharynx J Laryng 82 (1968) 393

GOLDMAN J L FRIEDMAN W H and BLOOM B S Elective neck dissection in laryngeal and laryngopharyngeal cancer J Laryng 78 (1968) 539

JONES Mc N R F The Paterson Brown Kelly syndrome Part I and II J Laryng 75 (1961) 529 and 544

JORGENSEN K Carcinoma of the larynx I Treatment mainly by primary irradiation *Acta* radiol Ther Phys Biol 9 (1970) 401

— and SELL A Carcinoma of the larynx II Treatment by ^{60}Co supervoltage irradiation Acta radiol Ther Phys Biol 10 (1971) 161

McCREA R S and DICKIE W R Carcinoma of the hypopharynx and cervical oesophagus A review of sixty one cases J Laryng 82 (1968) 421

NOHRMAN B A Survival rate calculation Acta radiol *39 (1953)* 78

OGURA J H and BILLER H F Pre operative irradiation for laryngeal and laryngopharyngeal cancers J Laryng 80 (1970) 802

SMITH R S FRAZEL E I CAULK R et coll The American Joint Committee s proposed method of stage classification and end result reporting applied to 1320 pharynx cancers Cancer 16 (1963) 1505

UICC Union Internationale Contre le Cancer Geneva 1968

WYNDER E L HULTBERG S JACOBSEN F and BROSS I J Environmental factors in cancer of the upper alimentary tract Cancer 10 (1957) 470

FROM THE GENERAL DEPARTMENT (DIRECTOR PROF E POPPE), THE NORWEGIAN RADIUM HOSPITAL, OSLO, NORWAY

RADIATION INJURY OF THE SPINAL CORD

by

Øyvin P Solheim

Radiation injury of the spinal cord is a rare complication in modern radiation therapy of malignant tumours There is a wide variation in the individual tolerance and the radiosensitivity of the cord is not always known with any accuracy, a certain risk of serious cord injury must therefore be accepted where exclusion of the cord from the irradiated volume would imply reduced chances of tumour destruction

Most previous reports emphasize a poor prognosis and the lesion has been termed chronic progressive radiation myelopathy This paper will suggest that the clinical course is not always chronic or progressive, but that considerable neuromuscular and sensory function may be regained

The case histories for all patients (1 654) admitted during the 14 year period 1956—1970 for carcinoma of the nasopharynx, tonsillae, larynx, thyroid and oesophagus were checked for information on pareses and when positive the corresponding records were examined Cases of proven or probable malignant infiltration of the nervous system and those with distant effects from malignant growths upon the neuromuscular system (neuromyopathia cancerogenes) were excluded Sensory symptoms during and shortly after irradiation were ignored

Four cases were disclosed by this procedure An additional case of pareses caused by irradiation for Hodgkin s disease was included in the material which thus consisted of a total of five cases

Submitted for publication 17 January 1971

Case reports

Case 1 A forty eight year old woman with squamous carcinoma of the hypopharynx and metastases to cervical lymph nodes was irradiated with 200 kV roentgen to four cervical fields one anterior and one posterior on each side of the neck each 14 cm×7 cm and 13 cm×6 cm The posterior fields were directed forwards so as to exclude the spinal cord However at that time the dose distribution was not calculated for each case and the posterior fields may have contributed to the cord dose Skin doses of 1 800 and 2 100 R were given to the anterior fields and 2 700 R to both posterior fields with a total of 17 fractions over 19 days The minimal cord exposure dose would have been 2 000 R and the maximal dose 4 700 R

Re examination after 2 4 and 7 months revealed no evidence of recurrence and no sign of spinal cord injury However seven months following the initial treatment an additional dose of 4 000 R to the hypopharynx with 200 kV rotation irradiation was applied The dose to the spinal cord was in the order of 3 200 R. Nineteen months after the first course of irradiation 12 months after the second course paresthesia developed in both arms and legs and progressive weakness followed When re admitted 24 months after the initial exposure the patient had moderate spastic quadripareses the gait was unsteady and crutches were necessary Hypesthesia was present below C4 and the sense of vibration was lost The Babinski sign was positive on both sides Roentgen examination of the cervical spine and a CSF examination demonstrated no abnormality myelography indicated severe arachnoiditis

One week later the first sign of improvement was noted with better muscular function in both hands Physiotherapy was applied and within one month the crutches were replaced by a stick The patient continued to get better slowly Five years after the initial irradiation re examination disclosed no pareses but some hypesthesia remained in the right leg Nine years after treatment the patient had no symptoms

Case 2 A forty eight year old woman was subjected to hemithyroidectomy and radical neck dissection for an undifferentiated carcinoma with regional lymph node metastases on the right side Each side of the neck was irradiated with a 3 600 R skin dose of 200 kV roentgen to 18 cm×12 cm fields The treatment was given with a total of 12 fractions over 13 days and the calculated dose to the spinal cord was 5 000 R Re examination after 2 3 6 and 11 months revealed no signs of recurrence metastases or cord injury

Fifteen months later herpes zoster developed in the left lower lumbar region Pain in the left was followed by weakness in the right leg Twenty months after irradiation a partial Brown Sequard syndrome was present with right hemiparesis and loss of sensations of heat and pain on the left side below Th8 The spinal fluid was normal and roentgen examination of the cervical spine failed to reveal metastases The patient was referred to physiotherapy

One month later repeat examination indicated general improvement of both the motor and the sensory systems The strength of movements of the right shoulder elbow and knee was only slightly reduced and there was no foot drop The sense of position was normal but the perception of temperature and pain on the left side of the body was still impaired The patient was re examined about every fifth month The improvement slowed down and ended after about 3 1/2 years She was then able to walk up and down stairs to dress and undress and differentiate between hot and cold with the left hand She was also able to do her own housework again The ability to walk on the toes or heels was regained

FROM THE GENERAL DEPARTMENT (DIRECTOR: PROF. E. POPPE), THE NORWEGIAN RADIUM HOSPITAL, OSLO, NORWAY

RADIATION INJURY OF THE SPINAL CORD

by

ØYVIN P. SOLHEIM

Radiation injury of the spinal cord is a rare complication in modern radiation therapy of malignant tumours. There is a wide variation in the individual tolerance and the radiosensitivity of the cord is not always known with any accuracy; a certain risk of serious cord injury must therefore be accepted where exclusion of the cord from the irradiated volume would imply reduced chances of tumour destruction.

Most previous reports emphasize a poor prognosis and the lesion has been termed chronic progressive radiation myelopathy. This paper will suggest that the clinical course is not always chronic or progressive, but that considerable neuromuscular and sensory function may be regained.

The case histories for all patients (1 654) admitted during the 14-year period 1956—1970 for carcinoma of the nasopharynx, tonsillae, larynx, thyroid and oesophagus were checked for information on pareses and when positive the corresponding records were examined. Cases of proven or probable malignant infiltration of the nervous system and those with distant effects from malignant growths upon the neuromuscular system (neuromyopathia cancerogenes) were excluded. Sensory symptoms during and shortly after irradiation were ignored.

Four cases were disclosed by this procedure. An additional case of pareses caused by irradiation for Hodgkin's disease was included in the material which thus consisted of a total of five cases.

Submitted for publication 17 January 1971.

Table

Five cases of late radiation myelopathy

Case No	Diagnosis	Dose to cord in R	Irradiation time	Latent period months	Progression period months	Improvement	Total observation time
1	Carcinoma of hypopharynx	2 000—4 700 + 3 200 after 7 months	19 days	19	5	Considerable	9 years
2	Carcinoma of thyroid	5 000	13 days	15	5	Considerable	6 years
3	Carcinoma of naso-pharynx	4 800	28 days	5	5	Considerable	4 years
4	Carcinoma of thyroid	5 000±500	22 days	6	4	Considerable	7 years
5	Hodgkin's disease	Less than 12 500	12 months	11	6	None	3 years

Case 5 A sixteen year old woman was given a series of irradiation courses over a period of 12 months for manifestations of Hodgkin's disease She had no neurologic signs before the irradiation Calculations indicated that because of field overlapping the total dose to the cervical cord may have reached a maximum of 12 500 R

Eleven months after the first course of neck irradiation two months after the last exposure the patient complained of hypesthesia of the lower part of the back and pareses of both legs developed One month later she was incapable of walking with pareses of the abdominal wall and both lower extremities Hypesthesia hypalgesia and hypthermesthesia were present below the chest. The pareses progressed until in a few weeks the legs were paralysed The neurologic signs then remained unchanged until the patient died three years after the initial treatment with gross manifestations in the chest of Hodgkin's disease Autopsy was not performed but the course of the neurologic signs was considered to be consistent with irradiation damage of the cord and not with malignant infiltration

Five women all irradiated for malignancy on fields that included the cervical cord developed different types of pareses and sensory deficiencies Malignant involvement of the central nervous system was not evident at any time in the course of the disease

The irradiation doses to the spinal cord ranging from more than 4 500 R to just under 12 500 R and the periods of time from the completion of the first course of irradiation to the initial signs of cord damage ranging from 5 to 19 months are listed in the Table This table also indicates that the period of

a slightly reduced strength of movements of the right hand and ankle and a reduction in the sense of pain and temperature however persisted The patient died six years after the initial treatment with lung metastases

Case 3 A forty five year old woman with Plummer Vinson syndrome developed undifferentiated carcinoma of the nasopharynx and was irradiated with 200 kV roentgen to four cervical fields one anterior and one posterior to each side of the neck the field sizes were 5 cm×12 cm and 5 cm×13 cm respectively the skin doses to all fields being 2 400 R with a total of 24 fractions over 28 days The calculated dose to the spinal cord was 4 800 R

Re examination two and four months later disclosed no signs of recurrence metastases or cord injury At about five months after irradiation the patient complained of progressive weakness of both legs and was admitted to hospital ten months after the irradiation Muscle strength was retarded in both lower extremities but spastic on the right side The gait was unsteady and the patient was not able to walk on the toes or heels The sense of position was lost and a greatly reduced sense of vibration was evident in both legs Perception of pain was lowered and no sense of temperature below the chest existed rectal incontinence was present Signs of metastases or recurrence were absent and the patient was discharged for physiotherapy at home

Sixteen months after irradiation the patient was re admitted markedly improved The motor system was normal except for slight retardation of movements of the right ankle She could walk ordinarily as well as on the toes and heels The sense of position and vibration was normal but a definite improvement in the perception of pain and temperature had not occurred Defecation was normal Lymph node metastases were however present and radical cervical dissection performed Twenty six months after irradiation perception of pain and temperature was regained The patient died after about four years with recurrence of the malignant growth of the neck

Case 4 A twenty five year old woman had a papillary thyroid carcinoma Subtotal thyroidectomy and bilateral paratracheal lymph node dissection were performed Post operative irradiation was given with 200 kV roentgen to four cervical fields one anterior and one posterior to each side of the neck Skin doses of 3 000 R were applied to all fields in 20 fractions over 22 days the calculated dose to the cord being 5 000±500 R Re examination after four months revealed no signs of recurrence metastases or injury to the cord

Six months after irradiation the patient noticed a reduced sense of heat in the left leg where weakness gradually developed When the patient was re admitted nine months after irradiation she was unable to walk Spastic pareses in the lower extremities and reduced muscular strength in both arms were evident Hypesthesia existed on the ulnar surface of both forearms and below the chest The patient was referred to physiotherapy One month later she was able to walk though with a spastic and atactic gait Some sense of vibration had returned in both legs There were no symptoms in the arms Three years after irradiation she could do ordinary housework She was admitted to hospital six years after treatment with increasing pain and reduced muscular strength of the right shoulder Slight pareses in both upper extremities and marked spastic pareses in both extremities were present The Babinski sign was positive on the left side the sensory levels appeared unchanged Some improvement in the condition but no signs of recurrence or metastases were evident Seven years after treatment the patient stated that she felt well although her legs were still spastic

cases occasionally appear in the literature (DYNES & SMEDAL 1960 Case 10) VAN DEN BRENK et coll (1968) reported that six out of 21 patients somewhat recovered It seems reasonable to refrain from offering another syndrome but to accept that the prognosis for slowly developing pareses after spinal cord irradiation is not always poor Some patients may benefit from an optimistic approach which includes physiotherapy The term chronic progressive radiation myelopathy should thus be avoided in the early period of changes

Steroids have been used to stop or reduce irradiation damage to the cord in the initial period of the disturbances (RUBIN & CASARETT 1968) The possibility demonstrated of spontaneous improvement in signs emphasizes that drug efficiency cannot be evaluated from isolated cases

Conclusions

Five cases of irradiation injury of the spinal cord are reported The irradiation doses to the cord and the latent periods were within the previously reported range Pareses and sensory disturbances progressed for a period of 5 to 6 months in four of the five cases a period of improvement followed The fifth patient who was the most seriously affected developed chronic neurologic signs All patients had had physiotherapy

The considerable improvement recorded in four of the five patients justifies a guarded optimistic attitude towards those who develop pareses following irradiation of the cord The term chronic progressive radiation myelopathy would not be apt at that stage The clinical course in these patients indicates that the effects of steroids and other drugs on the development of irradiation injury to the central nervous system sometimes recorded may be illusionary

SUMMARY

Five cases of late radiation myelopathy are reported Pareses and sensory disturbances progressed for some time after latent periods of from 5 to 19 months Four of the five cases were then considerably improved. The clinical course of late radiation myelopathy thus seems not always to be chronic or progressive

ZUSAMMENFASSUNG

Funf Falle einer spaten Strahlenmyelopathie werden besprochen Paresen und Sensibilitats storungen entwickelten sich nach Latenzperioden zwischen 5 und 19 Monaten Vier der funf Falle verbesserten sich wesentlich Der klinische Verlauf der spaten Strahlenmyelopathie scheint somit nicht immer chronisch oder fortschreitend zu sein

progress of signs in 4 of the 5 patients was about 5 months Physiotherapy was applied and a period of considerable improvement in the neurologic signs followed, however, the rate of improvement decreased gradually over a period of three to four years and various sequelae persisted

The condition of the fifth patient, in whom the signs were serious, did not alter

Discussion

The distribution of neurologic signs in the cases reported was in accordance with a lesion within the previously irradiated part of the spinal cord There were signs neither of malignant infiltration of the cord nor of a distant neoplasm that could have affected the neuromuscular system, negative findings that were verified by the course of the conditions The first signs of nerve injury appeared about 5 to 19 months after exposure to radiation The cases are therefore acceptable as being of late radiation myelopathy

Four of the five cases appeared in a group of 1 654 that had been exposed to cord irradiation The wide variations in the doses, the early deaths, and the numbers, prevent conclusions being drawn on the frequency of this complication of radiation therapy The cases do, however, represent a small percentage of the total number of those treated with similar or even higher doses to the spinal cord The doses of irradiation were within the previously reported range which seems heavily dependent upon the fractionation (ATKINS & TRETTER 1966) The period of time between the cord exposure and the appearance of initial nerve signs was also within the range previously given, that is 4 to 50 months (DYNES & SMEDAL 1960)

The development of signs progressed for less than 6 months in 4 of the 5 cases Subjective and objective improvement occurred in the following period, probably partly due to physiotherapy although it was also recorded before treatment of this kind The rate of improvement decreased gradually over a period of a few years and was followed by a chronic state

Symptoms and signs of radiation myelopathy have been grouped in the literature into different syndromes (1) transient radiation myelopathy (JONES 1964), (2) acute radiation myelopathy with progression within a few hours or days from the asymptomatic state to the completion of the neurologic deficit (BODEN 1950), and (3) chronic progressive radiation myelopathy (REAGAN et coll 1968) The present 5 cases could, in the period of progression, not be distinguished from previously reported cases of chronic progressive radiation myelopathy However in 4 of the 5 cases the course of the disease was neither chronic nor progressive for considerable improvement occurred after few months Similar

FROM THE DEPARTMENT OF GYNAECOLOGY (DIRECTOR: PROF. H. L. KOTTMEIER), RADIUMHEMMET, AND THE CENTRAL BACTERIOLOGIC LABORATORY OF STOCKHOLM CITY (DIRECTOR: PROF. T. PACKALÉN), STOCKHOLM, SWEDEN

LYMPHOCYTE STIMULATION BY THYROGLOBULIN AFTER LOCAL IRRADIATION OF THE THYROID GLAND IN MAN

by

NINA EINHORN, T. PACKALÉN and J. WASSERMAN

Radioiodine therapy is known to be followed by an increase in the circulating thyroid antibodies (BUCHANAN et coll. 1962, O'GORMAN et coll. 1964, IRVINE 1964, EINHORN et coll. 1965). A rise in antibodies to the thyroid cystoplasmic antigens but not to thyroglobulin has been observed in hyperthyroidism (EINHORN et coll. 1965, JONSSON et coll. 1968) and an increase in antibodies to both thyroid cytoplasmic antigens and thyroglobulin in euthyroid subjects treated by radioiodine (EINHORN et coll. 1966). This increase is temporary and lasts about a year after the radiotherapy (EINHORN et coll. 1965). The fact that surgical treatment for hyperthyroidism has been followed not by an increase but by a significant decrease in thyroid antibodies (HJORT & MOGENSEN 1962, EINHORN et coll. 1965) indicates that the increase observed after radioiodine therapy was related to local irradiation and not induced by the reduction in size of the thyroid gland or in the basal metabolic rate. The increase in thyroid

Submitted for publication 7 February 1971

RÉSUMÉ

Presentation de cinq cas de myelopathie radiotherapique tardive Apres une periode de latence allant de 5 a 19 mois les p ies et les troubles sensitifs ont progresse pendant un certain temps Puis quatre de ces c cas ont ete considerablement ameliores L evolution clinique de la myelopathie radiothe ique tardive parait donc ne pas etre toujours chronique ou progressive

F FERENCES

ATKINS H L and TRETTER P T dose considerations in radiation myelopathy Acta radiol Ther Phys Biol 5 (1966

BODEN G Radiation myelitis of th ain stem J Fac Radiol 2 (1950) 79

DYNES J B and SMEDAL M I Ra ion myelitis Amer J Roentgenol 83 (1960) 78

JONES A Transient radiation mye thy Brit J Radiol 37 (1964) 727

REAGAN TH J THOMAS J E and BY M Y Chronic progressive radiation myelopathy J Amer med Ass 203 (1968) 8

RUBIN PH and CASARETT G W ical radiation pathology Vol 2 p 623 W B Saunders Company, Philadelphia Lon and Toronto 1968

VAN DEN BRENK H A S RICHTER W and HURLEY R H Radiosensitivity of the human oxygenated cervical spinal cord based on analysis of 357 cases receiving 4 MeV X rays in hyperbaric oxygen Brit J Radiol 41 (1968) 205

Thyroglobulin was prepared ad modum WEIBULL & LINDER (1960) from human thyroid tissue removed at operation, several batches each from a single gland being used Tubes without antigens served as controls the total volume of the incubation mixtures was however always 1 0 ml The tubes were loosely closed with screw caps and incubated with a continuous flow of a mixture of 5 per cent carbon dioxide in air After 72 hours 0 4 μCi of ^{14}C thymidine was added to each tube and 24 hours later the tubes were cooled in ice water and washed twice in cooled buffer One drop of saturated ^{1} C thymidine was added to the first washing The washed cells were treated with 5 per cent TCA dissolved in 0 1 N sodium hydroxide and treated again with 6 7 per cent TCA After drying the pellets were dissolved in Soluene TM^{100} at 56° C Scintillation fluid was added to the aliquots of the dissolved samples and the radioactivity measured in a liquid scintillation spectrometer The uptake of ^{14}C thymidine in each sample was expressed in counts per minute and the means for duplicate tubes were taken The results were discarded whenever the counts in duplicate incubations varied more than 35 per cent The results were recorded as the ratio between the counts per minute obtained with and without antigen—the lymphocyte stimulation index (LSI)

Amounts of 10 100 1 000 or 5 000 μg of thyroglobulin were added to each tube in preliminary experiments (EINHORN et coll 1970) The highest stimulation of the DNA synthesis was observed usually in the tube to which 1 000 μg of thyroglobulin had been added but the difference from the values for the 100 μg tubes was mall and in 18 per cent of the cases these values were higher Since moreover the stimulation was never better with 5 000 than with 1 000 μg only preparations with 1 000 and 100 μg of thyroglobulin per tube were te ted thereafter In 40 ca es the values used are those for the 1 000 μg tubes and in 6 ca es—where at least one of the tests with the 1 000 μg tubes was unsuccessful—those for the tubes with 100 μg

Statistical methods The period after radiotherapy was divided into intervals corresponding as closely as possible to those for the routine clinical controls The results of the test for each interval were however not available for all the patients they had to be discarded in some tests because of the death of the lymphocytes or differences in counts in duplicate tubes, while in others the patients had not attended the routine examinations during the period prescribed for the investigation The patients were not recalled simply for new samples

The analysis included all the patients in whom the results of the test performed before the administration of the radioiodine and of at least one test after the radiotherapy were available

The statistical analysis was carried out by the usual methods including the Student s t test The difference in the index was obtained for each patient in

antibodies after local irradiation of the thyroid gland does not reflect a general rise in the autoimmune reactivity (JONSSON et coll 1968) An increase in antibodies to the irradiated tissues has also been recorded after irradiation of the vagina and uterus by locally applied radium (EINHORN et coll 1969) An increase in humoral antibodies to antigen present in the cell membrane of Burkitt's lymphoma and nasopharyngeal carcinoma was recently observed after radiotherapy in cases of these diseases in East Africa (EINHORN et coll 1970b)

The tissue damage in autoimmune states is considered to be due more to the cellular reactivity than to the circulating antibodies The response of lymphocytes to thyroglobulin was examined in vitro in patients with hyperthyroidism treated with radioactive iodine in order to ascertain the effect of local irradiation on the cell mediated immunologic reactivity to the irradiated tissue Thyroglobulin was chosen in preference to microsome antigen to keep allotypic differences to a minimum It has previously been reported that in 3 out of 8 cases of hyperthyroidism treated by ^{131}I the reactivity of the lymphocytes to thyroglobulin was higher than in any of 11 controls (EINHORN et coll 1970a)

Material and Methods

Lymphocyte donors The material consisted of 46 unselected consecutive patients with hyperthyroidism admitted for radiotherapy, 37 were women and 9 men, ranging in age from 29 to 78 years

The blood samples were obtained at regular clinical examinations to which the patients were submitted after radioiodine therapy The first control was performed 6 weeks to 3 months after administration of the radioiodine and repeated usually every 3 to 4 months during the first year A total of 180 successful tests were performed in these 46 patients

Laboratory methods The method for examining lymphocytic reactions to antigens in vitro relies on the fact that an increase in the incorporation of isotope labelled thymidine by the cells reflects an increase in the DNA synthesis in the presence of antigen (LING 1968)

About 50 to 100 ml of blood drawn from a cubital vein of the patients and controls were defibrinated by careful agitation with glass beads The lymphocytes were isolated ad modum COULSON & CHALMERS (1964) The cells were washed twice in Hank Tris buffer counted in a Burker chamber and suspended in Eagle s medium supplemented with 10 per cent of heat inactivated AB serum One or two million lymphocytes were pipetted into conical tissue culture tubes in a volume of 0 5 ml The antigens in appropriate concentrations were added to the cells in a volume of 0 5 ml

Table

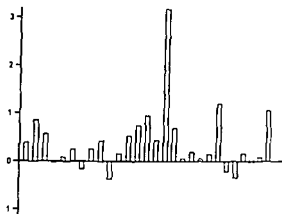
Lymphocyte stimulation by thyroglobulin before and after ¹³¹I therapy

Interval after ¹³¹I therapy	Number of patients	Change in the LSI* after ¹³¹I therapy number of cases		Mean of individual LSI differences		Level of significance for the difference p
		Increase	Decrease	Mean	SE	
6 weeks—3 months	28	23	5	+0.42	0.13	<0.01
4—6 months	30	16	13	+0.01	0.11	—
7—9 months	22	14	8	+0.01	0.11	—
10—12 months	21	9	12	+0.09	0.14	—
≥13 months	33	24	9	+0.23	0.10	<0.05

* Lymphocyte stimulation index

by an increase in cellular reactivity as reflected in the stimulability of the lymphocytes by a thyroid antigen, thyroglobulin.

The tests in this series were performed not earlier than 42 days after the administration of radioiodine. The period was chosen in the light of experience in an investigation of humoral antibodies in which an increase was present 2 to 12 months after radioiodine therapy (EINHORN et coll. 1965), but not before (EINHORN, FAGRAEUS & JONSSON, unpublished data). It is remarkable that the rise in the lymphocyte stimulation occurred early in the period, and it would be interesting to examine the reactivity of the lymphocytes even before 6 weeks after the supply of radioiodine. The reactivity of the lymphocytes to thyroglobulin was most marked 1.5 to 3 months after the irradiation; there was no significant increase 3 to 12 months after the radiotherapy. This does not exclude the possibility of increased cellular autoimmune reactivity having occurred during this period. Another and perhaps better method of examining cellular reactivity after local radiotherapy might be to test the delayed hypersensitivity to a thyroid antigen; such in vivo investigations in man are, however, complicated by the difficulty of preparing an antigen that entails no risk to the subject. Another promising approach might be to examine the lymphocytes in regional lymph nodes draining the irradiated tissues, although this was not possible in the present material. The results now reported are, however, in line with previous publications on the relationship of cellular immunity to circulating antibodies. It is firmly established that cellular immunity and antibody production are due to distinct mechanisms. Most investigations on the induction of cellular immunity suggest that the latter may be demonstrated before any circulating antibodies appear (SZENBERG et coll. 1967). Research in guinea pigs with autoimmune thyroiditis



Lymphocyte stimulation index in the presence of thyroglobulin 6 weeks to 3 months after radioiodine therapy for hyperthyroidism as compared to the index before therapy Each bar relates to one patient

the comparison between the lymphocyte stimulation before and after the radioiodine therapy The mean and the standard error of the mean were calculated for each series of these individual differences relating to each post therapy period, it was then determined whether this mean was significantly different from 0 00

Results

The geometric mean of the lymphocyte stimulation index for all the untreated patients with hyperthyroidism examined was 1 04, it did not differ significantly from 1 00 The index increased in 22, remained unchanged in 1 and decreased in 5 of the 28 patients tested before and 6 weeks to 3 months (42 to 91 days) after administration of the radioiodine (see the Figure), the mean was 1 01 ± 0 07 before and 1 43 ± 0 14 after radiotherapy The increase of 0 42 ± 0 13 is statistically significant ($p < 0\ 01$) It seemed to be larger for the 16 patients examined within 75 days than for those examined at 75 to 91 days (0 52 ± 0 12 against 0 28 ± 0 14), but the groups were too small to justify any conclusions In the patients examined within 75 days (42 to 75 days) the increase in the lymphocyte stimulation index was significant ($p < 0\ 05$) There was no significant increase in the lymphocyte stimulation in the patients examined 3 to 12 months after radiotherapy, but more than one year after radiotherapy there seemed again to be an increase in the lymphocyte stimulation This increase was relatively small but statistically significant ($p < 0\ 05$, see the Table)

Discussion

An increase in thyroid antibodies after local irradiation of the thyroid gland is recognized (BUCHANAN et coll 1962, O GORMAN et coll 1964, IRVINE 1964, EINHORN et coll 1965) Local irradiation of the gland seems also to be followed

ZUSAMMENFASSUNG

Die Lymphozytenstimulation durch Thyreoglobulin wurde bei 37 Fällen von Hyperthyreoidismus vor und nach lokaler Bestrahlung der Thyreoidea durch [131]I untersucht. Ein statistisch signifikanter Anstieg der Stimulation erfolgte zwischen 6 Wochen bis zu 3 Monaten.

RÉSUMÉ

Les auteurs ont étudié la stimulation lymphocytaire par la thyroglobuline dans 46 cas d'hyperthyroïdie avant et après irradiation locale de la glande thyroïde par [131]I. La stimulation lymphocytaire est augmentée de façon stastiquement significative entre six semaines à trois mois.

REFERENCES

Buchanan W. W., Koutras D. A., Crooks J. et coll.: The clinical significance of the complement fixation test in thyrotoxicosis. J. Endocr. 24 (1962) 115.

Coulson A. S. and Chalmers P. G.: Separation of viable lymphocytes from human blood. Lancet 1964: I, p. 468.

Einhorn J., Fagraeus A. and Jonsson J.: Thyroid antibodies after 131 treatment for hyperthyroidism. J. clin. Endocr. 25 (1965) 1218.

— — —: Thyroid antibodies in euthyroid subjects after iodine 131 therapy. Radiat. Res. 28 (1966) 296.

Einhorn N., Jonsson J. and Fagraeus A.: Immunologic reactions after irradiation of the uterus. Radiat. Res. 40 (1969) 465.

— Wasserman J. and Packalén T. (a): Cellular autoimmune reactions following radioiodine treatment for hyperthyroidism. Acta radiol. Ther. Phys. Biol. 9 (1970) 225.

— Klein G. and Clifford P. (b): Increase in antibody titer against the EBV associated membrane antigen complex in Burkitt's lymphoma and nasopharyngeal carcinoma after local irradiation. Cancer 26 (1970) 1013.

Hjort T. and Mogensen E. F.: Thyroid auto-antibodies. Acta med. scand. 171 (1962) 289.

Irvine W. J.: Thyroid auto immunity as a disorder of immunological tolerance. Quart. J. exp. Physiol. 49 (1964) 324.

Jonsson J., Einhorn N., Fagraeus A. and Einhorn J.: Organ antibodies after local irradiation. Radiology 90 (1968) 536.

Ling N. R.: Lymphocyte stimulation. North Holland Publishing Co. Amsterdam 1968.

O'Gorman P., Staffurth J. S. and Ballantyne M. R.: Antibody response to thyroid irradiation. J. clin. Endocr. 24 (1964) 1072.

Szenberg A. and Warner N. L.: The role of antibody in delayed hypersensitivity. Brit. med. Bull. 23 (1967) 30.

Wasserman J. and Packalén T.: Immune responses to thyroglobulin in experimental allergic thyroiditis. Immunology 9 (1965) 1.

Weibull C. and Linder L.: Preparation and properties of human thyroid globulin. Acta chem. scand. 14 (1960) 2036.

has revealed that cellular immunity to thyroglobulin appears before, and decreases earlier than, circulating antibodies (WASSERMAN et coll. 1965).

Although an increase in the humoral antibodies to thyroglobulin has been observed in euthyroid patients after radioiodine treatment (EINHORN et coll. 1966), such an increase in antibodies only to the cytoplasmic thyroid antigens (BUCHANAN et coll. 1962 and others) but not to the thyroglobulin (EINHORN et coll. 1965, JONSSON et coll. 1968) has been recorded in hyperthyroidism. A higher level of lymphocyte stimulation by thyroglobulin was apparent in hyperthyroid patients of the present material after radioiodine therapy.

Conclusions

An increase in the humoral antibodies occurs after local irradiation of the thyroid. In addition there is an increase in the cell mediated reactivity to a thyroid antigen, as reflected in the lymphocyte stimulation by thyroglobulin. The rise in stimulability of peripheral lymphocytes seems to be of shorter duration than the increase in the humoral antibodies; the available results cannot however determine whether the increase in the stimulability of lymphocytes occurs first. While the rise in humoral antibodies was confined to the cytoplasmic antibodies and in patients with hyperthyroidism did not extend to the antibodies to thyroglobulin, a higher degree of stimulation by thyroglobulin was evident in the present material.

An increase in humoral antibodies also takes place after local irradiation of benign (EINHORN et coll. 1969) and malignant (EINHORN et coll. 1970), tissue other than the thyroid tissue, but whether this applies to the cellular reactivity as well is not known. Nor is it established whether the increase in stimulability of lymphocytes observed has a bearing on the biologic effect of the radiotherapy. Combined clinical and immunologic investigations in individual cases may provide further information.

Acknowledgements

The authors take this opportunity of thanking Prof. J. Einhorn for his valuable guidance and Miss Eva Thulin for her excellent technical assistance. The work was supported by a grant from the Cancer Society of Stockholm.

SUMMARY

Lymphocyte stimulation by thyroglobulin was investigated in 46 cases of hyperthyroidism before and after local irradiation of the thyroid gland by ^{131}I. A statistically significant increase in the stimulation occurred at six weeks to three months.

ZUSAMMENFASSUNG

Die Lymphozytenstimulation durch Thyreoglobulin wurde bei 37 Fallen von Hyperthyreoidismus vor und nach lokaler Bestrahlung der Thyreoidea durch [131]I untersucht Ein statistisch signifikanter Anstieg der Stimulation erfolgte zwischen 6 Wochen bis zu 3 Monaten

RÉSUMÉ

Les auteurs ont etudie la stimulation lymphocytaire par la thyroglobuline dans 46 cas d hyperthyroidie avant et apres irradiation locale de la glande thyroide par [131]I La stimulation lymphocytaire est augmentee de façon stastiquement significative entre six semaines à trois mois

REFERENCES

BUCHANAN W W KOUTRAS D A CROOKS J et coll The clinical significance of the complement fixation test in thyrotoxicosis J Endocr 24 (1962) 115

COLLSON A S and CHALMERS P G Separation of visible lymphocytes from human blood Lancet 1964 I p 468

EINHORN J FAGRAEUS A and JONSSON J Thyroid antibodies after 131 treatment for hyperthyroidism J clin Endocr 25 (1965) 1218

— — — Thyroid antibodies in euthyroid subjects after iodine 131 therapy Radiat Res 28 (1966) ?96

EINHORN N JONSSON J and FAGRAEUS A Immunologic reactions after irradiation of the uterus Radiat Res 40 (1969) 465

— WASSERMAN J and PACKALEN T (a) Cellular autoimmune reactions following radioiodine treatment for hyperthyroidism Acta radiol Ther Phys Biol 9 (1970) 225

— KLEIN G and CLIFFORD P (b) Increase in antibody titer against the EBV associated membrane antigen complex in Burkitt s lymphoma and nasopharyngeal carcinoma after local irradiation Cancer 26 (1970) 1013

HJORT T and MOGENSEN E F Thyroid auto-antibodies Acta med scand 171 (196?) 289

IRVINE W J Thyroid auto-immunity as a disorder of immunological tolerance Quart J exp Physiol 49 (1964) 324

JONSSON J EINHORN N FAGRAEUS A and EINHORN J Organ antibodies after local irradiation Radiology 90 (1968) 536

LING N R Lymphocyte stimulation North Holland Publishing Co Amsterdam 1968

O GORMAN P STAFFURTH J S and BALLENTYNE M R Antibody response to thyroid irradiation J cl n Endocr 24 (1964) 1072

SZENBERG A and WARNER N L The role of antibody in delayed hypersensitivity Brit med Bull 23 (1967) 30

WASSERMAN J and PACKALÉN T Immune responses to thyroglobulin in experimental allergic thyroiditis Immunology 9 (1965) 1

WEIBULL C and LINDER L Preparation and properties of human thyroid globulin Acta chem scand 14 (1960) 2036

has revealed that cellular immunity to thyroglobulin appears before, and decreases earlier than, circulating antibodies (WASSERMAN et coll 1965)

Although an increase in the humoral antibodies to thyroglobulin has been observed in euthyroid patients after radioiodine treatment (EINHORN et coll 1966), such an increase in antibodies only to the cytoplasmic thyroid antigens (BUCHANAN et coll 1962 and others) but not to the thyroglobulin (EINHORN et coll 1965, JONSSON et coll 1968) has been recorded in hyperthyroidism A higher level of lymphocyte stimulation by thyroglobulin was apparent in hyperthyroid patients of the present material after radioiodine therapy

Conclusions

An increase in the humoral antibodies occurs after local irradiation of the thyroid In addition there is an increase in the cell mediated reactivity to a thyroid antigen, as reflected in the lymphocyte stimulation by thyroglobulin The rise in stimulability of peripheral lymphocytes seems to be of shorter duration than the increase in the humoral antibodies, the available results cannot however determine whether the increase in the stimulability of lymphocytes occurs first While the rise in humoral antibodies was confined to the cytoplasmic antibodies and in patients with hyperthyroidism did not extend to the antibodies to thyroglobulin, a higher degree of stimulation by thyroglobulin was evident in the present material

An increase in humoral antibodies also takes place after local irradiation of benign (EINHORN et coll 1969) and malignant (EINHORN et coll 1970), tissue other than the thyroid tissue, but whether this applies to the cellular reactivity as well is not known Nor is it established whether the increase in stimulability of lymphocytes observed has a bearing on the biologic effect of the radiotherapy Combined clinical and immunologic investigations in individual cases may provide further information

Acknowledgements

The authors take this opportunity of thanking Prof J Einhorn for his valuable guidance and Miss Eva Thulin for her excellent technical assistance The work was supported by a grant from the Cancer Society of Stockholm

SUMMARY

Lymphocyte stimulation by thyroglobulin was investigated in 46 cases of *hyperthyroidism* before and after local irradiation of the thyroid gland by ^{131}I A statistically significant increase in the stimulation occurred at six weeks to three months

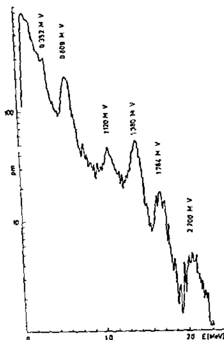


Fig 1 Complex spectrum of incorporated ^{226}Ra in man

Material and Method The possibility of determining the retained Ra and Rn directly from the spectrum measured in the experimental animal is demonstrated in Figs 1 and 2 If Ra is at a low degree of equilibrium with its products (< 50 per cent) or if not a strongly scattering medium the 187 keV line may well be recorded in spite of its origin from a 50 per cent conversion with a mere six per cent probability of emission As absolute deemanation is not practicable even the slightest activity of daughter products affects the 187 keV line by Compton scattering and direct quantitative evaluation is only possible if this superposition is deducted As reported previously this may be carried out because the ratio of the counting rate pertaining to the Compton effect in the band of the 187 keV line to the counting rate recorded in the 1764 keV band must be constant It is quite sufficient for calibration to carry out several measurements and to calcute the relation R from linear equations of the type

$$N = A + RN_1$$

where N_1 and N are the counts measured in the region of the gamma ray lines 1764 and 187 keV respectively and A is the counting rate in the energy band of 187 keV due to pure Ra

MEASUREMENT OF ^{226}Ra IN MICE

by

V LENGER

Investigations of the dose response relationship of certain bone seeking nuclides suggested that the problem of the rapid and sufficiently precise measurement of ^{226}Ra activities in injections should be solved It also appeared desirable to follow up dynamic changes of this nuclide in experimental animals, for example, mice, in which it is impossible to achieve equilibrium and in which the fraction of expired radon is unknown The amount of ^{226}Ra activity is usually ascertained by measurement of the gamma RaC (^{214}Bi) activity in equilibrium The same lines of RaC (^{214}Bi) deposited in the body of the subject measured are mostly used in measuring incorporated activities in vivo and the results achieved corrected by the Rn emanating fraction The period required for establishment of equilibrium is a hindrance and the procedure described is only accurate if the assumption is correct that the amount of radon exhaled by the object measured equals the amount released from radium deposits in the body The uncertainty of this assumption causes the results to be considerably weighted

LENGER & THOMAS (1971) attempted to explain the new spectrometric method of measuring ^{226}Ra activity in a nonequilibrium state consisting in the regression analysis of the time course of counting rates in the 187 keV emitted from the ^{226}Ra and 1764 keV emitted from RaC (^{214}Bi) bands This method was applied in the undermentioned measurement in mice with ^{226}Ra incorporated in vivo

Submitted for publication 11 November 1970

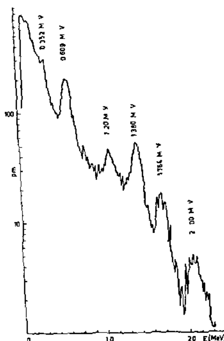


Fig 1 Complex spectrum of incorporated ^{226}Ra in man

Material and Method The possibility of determining the retained ^{226}Ra and ^{222}Rn directly from the spectrum measured in the experimental animal is demonstrated in Figs 1 and 2 If ^{226}Ra is at a low degree of equilibrium with its products (< 50 per cent) or if not a strongly scattering medium the 187 keV line may well be recorded in spite of its origin from a 50 per cent conversion with a mere six per cent probability of emission As ab olute deemanation is not practicable even the slightest activity of daughter products affects the 187 keV line by Compton scattering and direct quantitative evaluation is only possible if this superposition is deducted As reported previously this may be carried out because the ratio of the counting rate pertaining to the Compton effect in the band of the 187 keV line to the counting rate recorded in the 1764 keV band must be constant It is quite sufficient for calibration to carry out several measurements and to calcute the relation R from linear equations of the type

$$N_2 = A + RN_1$$

where N_1 and N_2 are the counts measured in the region of the gamma ray line 1764 and 187 keV respectively and A is the counting rate in the energy band of 187 keV due to pure ^{226}Ra

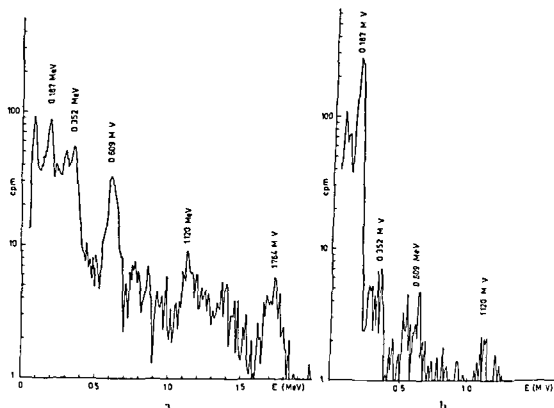


Fig. 2. a) ^{226}Ra spectrum in mice 205 days after single administration. b) ^{226}Ra spectrum in mice 10 minutes after single administration.

The precision may be controlled by determining that $R = \text{const}$.

The mice injected with ^{226}Ra were divided into groups of ten. This number was *limited by the geometry with the compromise that the angular dependence* should be of the least possible effect and that the sensitivity should be relatively high at a comparatively short period of measurement (15 minutes). Coaxial arrangement of the two scintillation crystals NaI (Tl) 5 × 4″ (12.5 cm × 10 cm) was decided upon to balance the effect of nonhomogeneous distribution.

Quantitative evaluation made it necessary to carry out calibration measurements. In principle one of the two methods known in the problem of in vivo measurement, could be applied. It was possible to apply the known amount of radioactive substance in one. However, due to the kinetics and the metabolism of the members of the series it was difficult to control the degree to which the Compton scattering contributed in the band of the 187 keV line. A phantom *in* which the system of non uniformly distributed activity in strongly heterogeneous medium was replaced by a physically simpler and better defined system was therefore *constructed. The accuracy of this phantom is imperative if the evalu-*

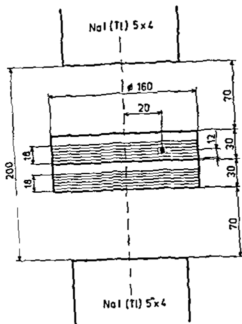


Fig 3 Phantom used for calibration Each cylinder held 10 mice during the experiments

ation is to be correct and precise The basic part of the phantom con isted of a cylindrical container into which the mice with the radium injected were placed the ba ic dimensions were thus fixed It was necessary to decide upon the optimal position of the reference source and upon the quality and amount of the scattering medium The container was designed for effective ventilation during the measurement so that the exhaled radon was expelled

It was decided to experiment with mice of 40 g live weight the expected maximum (The lowest limit was laid down as 20 g) Experience with similar phantoms in spectrometric evaluation of whole body activities in man suggested the use of Masonite (lg cm⁻³) and approximation of the quasipoint secondary standard (WENGER et coll 1968) Because it was necessary to expect migration of one or several mice should die it would not have been correct to place the reference source mentioned into the centre of the geometry For this reason a point was selected that represented the mean yield from the central and marginal position of the mou e in the container The reference source of ²²⁶Ra was measured for this purpose in equilibrium in a sealed ampoule at the edge and centre of the container The spatial angle was related to the effective centre of the crystal Counts in the band of 187 keV line differed in these cases by 25 per cent By projecting the i ocounts curves obtained into a level vertical to the

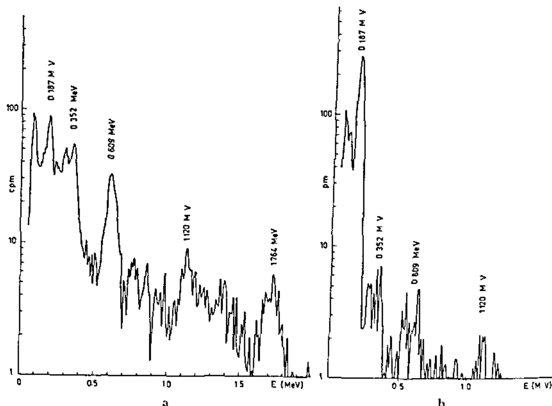


Fig. 2. a) ^{226}Ra spectrum in mice 205 days after single administration. b) ^{226}Ra spectrum in mice 10 minutes after single administration.

The precision may be controlled by determining that $R =$ const.

The mice injected with ^{226}Ra were divided into groups of ten. This number was limited by the geometry with the compromise that the angular dependence should be of the least possible effect and that the sensitivity should be relatively high at a comparatively short period of measurement (15 minutes). Coaxial arrangement of the two scintillation crystals NaI (Tl) 5 × 4″ (12.5 cm × 10 cm) was decided upon to balance the effect of nonhomogeneous distribution.

Quantitative evaluation made it necessary to carry out calibration measurements. In principle, one of the two methods known in the problem of in vivo measurement, could be applied. It was possible to apply the known amount of radioactive substance in one. However, due to the kinetics and the metabolism of the members of the series it was difficult to control the degree to which the Compton scattering contributed in the band of the 187 keV line. A phantom in which the system of non uniformly distributed activity in strongly heterogeneous medium was replaced by a physically simpler and better defined system was therefore constructed. The accuracy of this phantom is imperative if the evalu

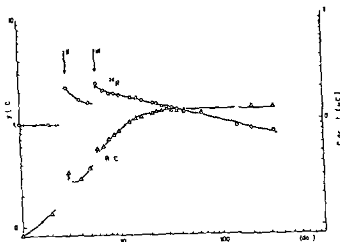


Fig 6 ²²⁶Ra retention curve for mice after triple administration (dotted line is the assumed trend)

effect of the energy difference between ^{57}Co 122 keV and ^{226}Ra 187 keV was taken into consideration when the true value of the area density (or the cross section) was ascertained The values thus obtained could then be easily substituted by an artificial absorber in the present case by Masonite The arrangement is demonstrated in Fig 3

Results

The model thus constructed was used for a series of calibration measurements (Fig 4) The latter were processed according to the linear equations mentioned and the constant $R = 3\,84 \pm 0\,05$ was calculated The calibration curves or the value of the R constant count only for a single arrangement (geometry and absorbing medium) If the activity of an unknown sample is to be determined one measurement will suffice if the counts in the 187 keV and 1764 keV bands are known The respective counting rate of ^{226}Ra and thus also its activity may then be obtained with the help of R The retention curves measured by the method described are plotted in Figs 5 and 6 their biologic importance will be discussed in a separate paper

The kinetics of ^{226}Ra immediately after its injection at different states of equilibrium were investigated for the biologic interpretation of the results A solution of ^{226}Ra in equilibrium was injected into the mouse intraperitoneally — this being a marginal case The mouse was placed in a container in which

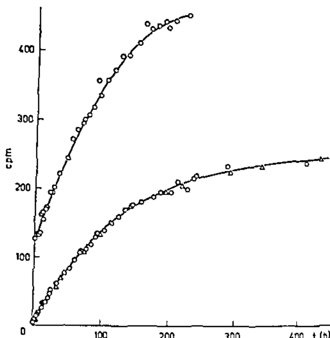


Fig. 4. Calibration curves. The upper curve denotes the time course of counts in the 187 keV line band including Compton scattering, the lower curve being the time course of RaC (^{214}Bi). (Δ denotes the theoretic values)

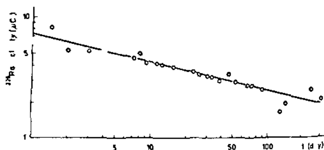


Fig. 5. ^{226}Ra retention curve for mice with single administration

window of the crystal, the active centre was determined, i.e. the point at a certain distance from the centre of the system where the counting rate measured was identical with the mean value measured in the regions and marginal positions mentioned.

The area density of the average mouse had to be known in order to ascertain the quantitative effect of the absorbing and scattering matter, in this case Masonite. A point source of ^{57}Co (122 keV gamma rays) was therefore measured below and above, and in contact with the anaesthetized mouse. The mean counting rates of these measurements were compared with values measured with the same geometry in air. The difference in these values corresponded to the effect to the absorption of the point source localized in the mouse. By transferring this difference into the relation of absorption obtained for the same emitter in similar geometry, the area density of the complex tissue in mice was obtained. The

Table

heck on the reliability of the method A mineralized mice individually B mineralized mice individually in equilibrium

Measurement	Counting rate (cpm) in the band		Activity (μCi)
	187 keV	1764 keV	
A	2473	200	0 0303
	2154	116	0 0?6?
	?573	174	0 0292
	3015	218	0 0334
	2679	131	0 0334
		Total	0 153
B			0 0332
			0 0?53
			0 0337
			0 03?9
			0 0353
		Total	0 160

It is evident that the error amounts to 3 1 per cent although the experiment covers three different geometries (5 mice in vivo × 1 ampoule in phantom × 1 ampoule in the air in the axis of the crystal) The reproducibility was ascertained from measurements of 10 mice at the 240 and 251 day after injection The mean was calculated from $^{?}$Ra and RaC (^{14}Bi) values for ten measurements the standard deviation and the relative error being calculated according to normal relations The square of relative errors from the statistics of radioactive decay was subtracted from the squares of relative errors for ^{6}Ra and RaC (^{14}Bi) The resulting relative error thus includes for both isotopes the effect of the geometry variation and the stability of measurement conditions for both isotopes for $^{?}$Ra this error amounts to ± 3 4 per cent and for RaC (^{14}Bi) ± 0 9 per cent

SUMMARY

Low Compton scattering affords means of direct measurement of the ^{6}Ra 187 keV line the quantitative evaluation being based on the phantom calibration procedure The non equilibrium state is an advantage The retention curves of ^{6}Ra in mice during a period of up to 352 days are presented and the kinetics of daughter products especially of Rn proved

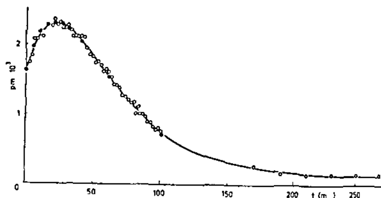


Fig 7 The time change of RaC (^{214}Bi) in mice after single application of ^{226}Ra in equilibrium (filled circles denote the theoretic values)

ventilation was efficiently solved by a double stream of air to prevent interference by the exhaled radon fraction and its daughter products The first measurement was made at two minutes, the evaluation being performed in the bands of 187 keV and 1764 keV lines There was no excretion by the mouse during the measurement so that the effect of radon exhalation and that of decay and increase of the individual daughter products of radon could be observed

It is interesting that kinetic equilibrium occurs only as late as 4 hours after administering ^{226}Ra in equilibrium The most important of the curves obtained (Fig 7) indicates the trend of RaC (^{214}Bi) as the time function This is caused by *the superposition of the decay Ra/B+C/ and the growing of RaC* (^{214}Bi) out of RaB The right descending branch plots the transient equilibrium The RaC (^{214}Bi) trend was calculated to prove the relations measured under the assumption that the Rn retention is zero and that the RaA incorporation is also negligible (RaA = 0) This theoretic trend is practically identical with the curve measured and is therefore sufficient proof of a rapid exhalation of radon The practical importance of this finding is apparent when the uncertainty in measuring an experimental animal immediately after it has been treated is considered

The reliability of the method was verified by measurement of five experimental objects — mice in which unknown ^{226}Ra activity was injected intraperitoneally At first all five mice were measured collectively during an unknown time after the administration The mice were then killed and mineralized, the mineralisate being sealed and measured individually in a nonequilibrium state (Table A) After establishing equilibrium the ampoules containing the mineralisates were again measured (B) The evaluation of these last measurements were carried out by comparing the 1764 keV line with the standard

IROM ST ELIZABETH S HOSPITAL TUFTS MEDICAL SCHOOL BOSTON MASSACHUSETTS
USA

EFFECTS OF RADIATION AND HYPOXIA ON THE METABOLIC FATE OF ERYTHROPOIETIN

by

ALBER O OSVALDO CARMENA

The metabolic fate of erythropoietin is poorly understood STOHLMAN & BRECHER (1959) sugge ted that pla ma levels of erythropoietin depended upon the state of bone marrow function NAETS & WITTEK (1968 1969), rejected the idea that differentiated erythroid cells influence metabolism similar results have been reported by BOZZINI (1966) Since both arguments are inconclusive an investigation into the relationship between the bone marrow cellularity and the circulating erythropoietin in rats submitted to hypoxia and ionizing radiations was performed

Material and Methods Six groups of male Sprague Dawley rats 10 to 12 weeks old were investigated (1) twenty normal rats at sea level, (2) twenty rats submitted for 24 hours to 19 000 feet (3) twenty four rats irradiated with 200 R whole body irradiation and kept at 19 000 feet for 24 hours (4) twenty four rats irradiated with 200 R and sacrificed 24 hours later (at ea level) (5) twenty rats kept at 19 000 feet for seven days and (6) twenty rats kept at 19 000 feet for seven days and irradiated with 200 R on the sixth day of hypoxia (see Fig 1)

Submitted for publication 28 May 1970 A O C is now at Department of Physiology Ho pital E Cabrera Habana Cuba

ZUSAMMENFASSUNG

Niedrige Compton Streuung gestattet direkte Messungen der ²²⁶Ra 187 keV Linie deren quantitative Berechnung sich auf Phantom Kalibrierungen stutzt Der Nicht Gleichgewichts zustand ist ein Vorteil Die Retentionskurven von ²²⁶Ra in der Maus wahrend einer Periode bis zu 352 Tagen werden gegeben und die Kinetik der Tochterprodukte besonders von Rn, dargelegt

RÉSUMÉ

La diffusion Compton de faible energie fournit un moyen de mesure directe de la ligne de 187 keV du ²²⁶Ra, l évaluation quantitative etant basee sur la technique d etalonnage sur fantome L etat de non équilibre est un avantage L auteur presente les courbes de retention de ²²⁶Ra sur des souris pendant une periode allant jusqu a 352 jours il montre la cinetique de ces produits descendants en particulier du ²²²Rn

REFERENCES

LENGER V and THOMAS J Determination of ²²⁶Ra activity i nonequilibrium state by gamma scintillation spectrometry Nucl instr Meth 91 (1971) 247

WENGNER P, BENGTSSON L G DUDLEY R A et coll Whole body counting of persons containing ⁹⁰Sr and ²²⁶Ra An interlaboratory comparison Hlth Phys 14 (1968) 209

Table 1

Hematocrit hemoglobin and reticulocyte values in rats submitted to hypoxia alone irradiation alone and hypoxia and irradiation Hx hypoxia (±) standard error

Groups	Hematocrit	Hemoglobin g	Ret culocytes (mm) × 10
1 (Normals)	40 3±0 5	12 3±0 16	2 08±0 13
2 (24h H)	44 3±0 9	14 4±0 3	3 06±0 31
3 (24h Hx + 200R)	42 5±0 6	13 1±0 2	1 54±0 25
4 (Sea level 24h + 200R)	39 5±0 6	11 4±0 4	0 58±0 15
5 (7d Hx)	53 9±1 0	18 2±0 4	4 51±0 36
6 (7d Hx + 200R)	54 5±1 0	18 1±0 2	2 12±0 39

Table 2

Erythroblasts in bone marrow and spleen with spleen weights Hx hypoxia (±) standard error

Groups	Eryth oblasts ( )		Spleen weight (g)
	Bone marrow	Spleen	
1 (Normals)	24 7±1 5	3 5 ±0 5	0 637±0 05
2 (24h Hx)	26 5±1 8	2 4 ±0 5	0 498±0 06
3 (24h Hx+200 R)	10 0±1 9	1 0 ±0 4	0 298±0 03
4 (Sea level 24h+200R)	6 7±1 1	0 17±0 13	0 342±0 01
5 (7d Hx)	33 3±1 3	5 7 ±0 8	0 672±0 09
6 (7d Hx+200R)	14 6±2 0	1 3 ±0 4	0 257±0 02

Table 3

Units of erythropoietin per ml of plasma injected subcutaneously in fasting rats Hx hypoxia (±) standard error

Groups	Units of erythropoiet n per ml of plasma
1 (Normal)	0
2 (24h Hx)	2 1±0 5
3 (4h Hx+200R)	4 0±0 8
4 (Sea level 24h+200R)	0
5 (7d Hx)	0
6 (7d Hx+200R)	2 2±0 5

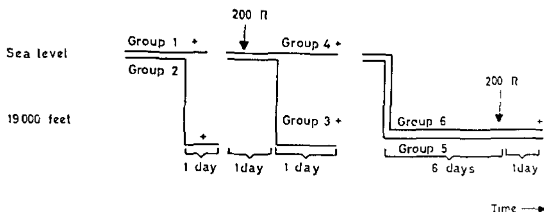


Fig 1 Working scheme + day of sacrifice

Rats exposed to hypoxia for seven days were kept in the barometric chamber for 23 hours daily, one hour was reserved to clean the cages and change the food and water The animals were sacrificed by cardiac puncture under ether The following controls were performed, hematocrit, reticulocyte, hemoglobin, red blood cell counts with a Coulter Counter Model B and bone marrow femur smears were made by the brush technique and no less than one thousand nucleated cells were counted The spleens were weighted, imprints were made and no less then one thousand cells were counted The plasma of these animals *was separated by centrifugation at 3 000 rpm for 30 minutes in a cold centrifuge* The fasting rat test was used Sprague Dawley female rats, 8 to 12 weeks old were kept without food and at the second and third day of fasting two ml/day/ rat injected subcutaneously and on the fourth day 0 5 μCi ^{59}Fe introduced intravenously The animals were sacrificed 24 hours later by cardiac puncture under ether Hematocrit, reticulocyte and ^{59}Fe incorporation in the red blood cells tests were performed, assuming a blood volume of 5 ml per 100 g body weight The erythropoietic activity of the injected plasmas was expressed in units of erythropoietin per ml, withdrawn from a dose response curve of erythro poietin Standard B

Results

The peripheral values of the different groups indicated an increase in hema tocrit reticulocyte and hemoglobin values after seven days of hypoxia (Table 1) Reticulocytes were significatively reduced in the irradiated groups The per centage of erythroblasts in bone marrow and spleen also followed this pattern

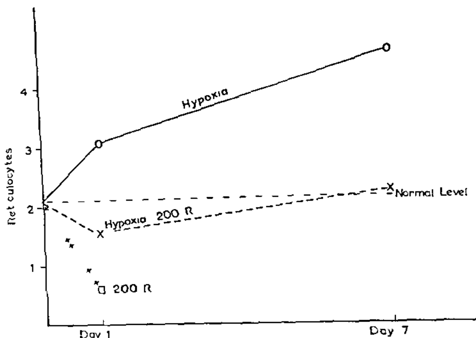


Fig 3 Number of reticulocytes per mm³

The results reinforce the hypothesis of STOHLMAN & BRECHER (1959) in the sense that erythropoietin is used or degraded by the erythroid tissue This hypothesis is also supported by the works of HAMMOND & ISHIKAWA (1962) who demonstrated that the rate of disappearance of erythropoietin from the plasma was faster in patients with hemolytic anemia than in those with hypoplastic anemia after blood transfusion JACOBSON et coll (1959) were of the same opinion The author has detected erythropoietin in the plasma of dwellers at 14 900 feet who descended to sea level at up to 42 hours due probably to a failure in the utilization of the hormone by hypoplastic bone marrow The contradictory results of NAETS & WITTEK (1968 1969) and BOZZINI (1966) could be due to the animal employed The bone marrow of the dog is not affected by hypertransfusion as in other mammals (STOHLMAN) and at 14 000 feet does not respond to hypoxia unless the animal is subjected to exercise (PACE)

It would appear that the presence of erythropoietin in plasma is in inverse relationship to the cellularity of the erythroid bone marrow

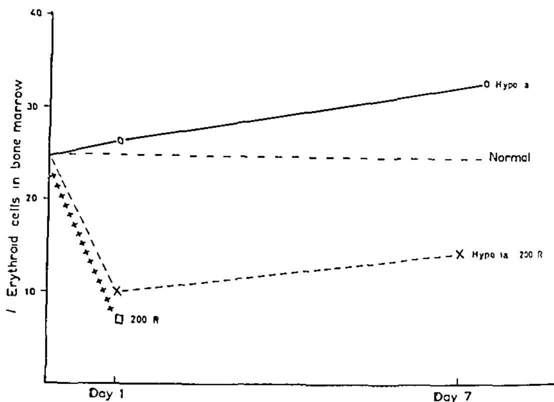


Fig 2 Percentage of erythroid cells in bone marrow in rats subjected to hypoxia alone irradiation alone and hypoxia and irradiation

(Table 2) The size of the spleens was reduced in the irradiated groups After 24 hours of hypoxia, 2 1 units of erythropoietin were present, but at the seventh day the plasma revealed no erythropoietic activity (Table 3) The irradiated animals in hypoxia increased in erythropoietic plasma content

Discussion

Hypoxia induces an increase in bone marrow erythroid precursors that is followed by reticulocytosis (Figs 2 3) Two hundred R reduce the percentage of erythroblasts in bone marrow even in the presence of the hypoxic stimulus (Figs 2, 3 and Table 2) Circulating erythropoietin is increased twofold at one and 7 days of hypoxia in irradiated rats (Fig 4) The author was unable to demonstrate erythropoietin at the seventh day of hypoxia in non irradiated animals This was also observed in the urines of human subjects exposed to 13 127 feet (CARMENA 1964) and 14 900 feet (CARMENA et coll 1967)

ZUSAMMENFASSUNG

Spragu Dawley Ratten wurden verschiedene Zeit lang in 19 000 Fuss gehalten Die Tiere die eine Ganzkorperbestrahlung von 200 R erhalten hatten hatten einen signifikanten Anstieg des Plasmaerythropoietins Es wird gefolgert dass der Erythropoietinspiegel in einem umgekehrten Verhaltnis zur Zellularitat der erythroiden Prakusoren steht

RÉSUMÉ

D s rats Sprague Dawley ont eté maintenus à 19 000 pieds pendant differentes periodes Les animaux qui ont reçu une irradiation totale du corps de 200 R ont présenté une elevation significative de l erythropoietine plasmatique L auteur conclut que le taux d erythropoietine est en relation inverse du nombre des cellules des précurseurs érythroides

REFERENCES

BOZZINI C E Influence of the erythroid activity of the bone marrow on the plasma disappearance of injected erythropoietin in dogs Nature 209 (1966) 1140

CARMENA A O Métodos de dosaje de la actividad eritropoyética del plasma usando receptores humanos (In Spanish) Rev Soc argent Biol 40 (1964) 110

— GARCIA DE TESTA N and FRIAS F L Urinary erythropoietin in men *subjected to acute* hypoxia Proc Soc exp Biol 125 (1967) 441

— GARCIA N E AGGIO M C y COHEN TARICA J Estudio de la eritropoyetina plasmática en residentes de 4 540 metros de altura en los primeros dias de descenso a nivel del mar (In Spanish) Rev Soc *argent Biol 40 (1964) 107*

HAMMOND D and ISHIKAWA A The rate of disappearance of erythropoietin following transfusion of severely anemic patients *In* Erythropoiesis p 128 Grune & Stratton New York 1962

JACOBSON L O GOLDWASSER E and GURNEY C W Control of red cell formation *In* The kinetics of cellular *proliferation* p 344 Grune & Stratton New York 1959

NAETS J P and WITTEK M Effect of *erythroid hyperplasia* on the disappearance rate of erythropoietin in the dog Acta haemat 39 (1968) 42

— — Erythropoietic activity of marrow and disappearance of erythropoietin in the rat Amer J Physiol 217 (1969) 297

PACE N Personal communication

STOHLMAN F Observations on the physiology of erythropoietin and its role in regulation of red cell production Ann N Y *Acad Sci 77 (1959) 710*

— Personal communication

— and BRECHER G Humoral regulation of erythropoiesis V Relationship of plasma erythropoitin level to bone marrow activity Proc Soc exp Biol 100 (1959) 40

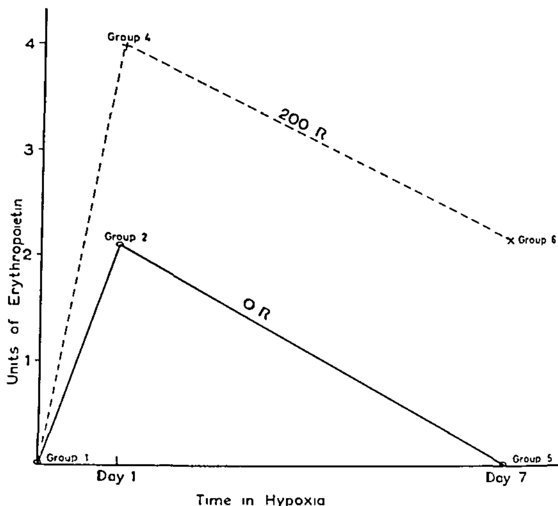


Fig 4 Units of erythropoietin per ml of plasma injected in fasting rats

Acknowledgement

This work was supported in part by the U S Public Health Service and the National Heart Institute

SUMMARY

Sprague Dawley rats were kept at 19 000 feet for various periods The animals that received 200 R whole body irradiation had a significantly increased plasma erythropoietin It is concluded that the levels of erythropoietin are in inverse relationship to the cellularity of the erythroid precursors

where

- D_w is the absorbed dose in water at the position of the measurement point of the chamber when the chamber is replaced by water and an identical irradiation given rad
- $k_{^{60}Co}$ is the ^{60}Co exposure calibration factor of the chamber at a specified temperature and pressure of the air determined in free air at SSD 100 cm and field size 10 × 10 cm when a 4 mm thick build up cap of perspex is used, R/div
- M is the instrument meter reading corrected for general recombination and corrected to air at the same temperature and pressure div

SVENSSON & PETTERSSON (1967) presented experimentally determined absorbed dose calibration factors k for different electron beam energies and for different phantom depths along the central ray They showed that for one particular chamber the factors were independent of field size collimation and SSD in the range 5 to 30 MeV of primary electron energy within experimental uncertainties The calibration factors were also applicable to different betatrons (SVENSSON 1971) The purpose of the present investigation was to determine absorbed dose calibration factors for several types of commercial chambers at the point of peak absorbed dose for different electron beam energies The influence of several correction factors which depend on the chamber construction are discussed The properties of a chamber suitable for absorbed dose measurements in electron beams are summarized and absorbed dose calibration factors for an ideal thimble ionization chamber given

Experiments

Energy calibration of electron beam In the present investigation a Brown Boveri 35 MeV betatron was used The energy of the electrons incident on the phantom surface E_o (MeV) was determined from the relation by SVENSSON & HETTINGER (1971)

$$R_p = k_1 \quad E - k$$

where

- R_p is the practical extrapolated range determined from depth ionization curves in water cm
- k_1 0 520 MeV^{-1} cm
- k_2 0 26 cm

The decrease in the mean energy of the primary electrons within the phantom was assumed to follow the relation given by HARDER (1965)

FROM THE RADIATION PHYSICS DEPARTMENT (DIRECTOR PROF G HETTINGER),
UNIVERSITY OF UMEA, SWEDEN

COMMERCIAL THIMBLE CHAMBERS FOR ABSORBED DOSE MEASUREMENTS AT HIGH ENERGY ELECTRON RADIATION

by

H SVENSSON, C PETTERSSON and G HETTINGER

Electron radiation from betatrons is to an ever increasing extent used for radiotherapy A simple, generally accepted method for measuring the absorbed dose of high energy electron radiation does not yet exist For ^{60}Co γ radiation there are, however, well established methods for measuring exposure and absorbed dose

The Hospital Physicists Association (HPA) (1969) has recommended a Code of Practice for the determination of absorbed dose of high energy photon radiation based on the use of thimble chambers exposure calibrated at ^{60}Co γ radiation or 2 MV roentgen rays The International Commission on Radiation Units and Measurements (ICRU) Report No 14 (1969) has adopted the HPA method Similar methods for electron radiation have been suggested by ALMOND (1967, 1970), SVENSSON & PETTERSSON (1967) The latter authors defined absorbed dose calibration factors k of the thimble chambers that convert the instrument reading to absorbed dose in water according to

$$D_w = k_{^{60}Co} \cdot M \cdot k$$

Submitted for publication 13 July 1970

Table 1

Absorbed dose calibration factors for different commercial thimble ionization chambers SSD = 100 cm Field size 8 × 10 cm ≈ 5 cm stem irradiation

Type of thimble ionization chamber	Volume (cm^3)	Absorbed dose calibration factors k				
		E/MeV	30.4	22.8	13.2	8.5
		d/cm	2.0	2.0	1.5	1.5
		E_m/MeV	26.4	18.8	10.2	5.5
Philips type 37480/10 No 1644	3.0		0.807	0.827	0.868	(0.927)*
Philips type 37480/10 No 1589	3.0		0.807	0.833	0.875	(0.936)*
Baldwin Farmer No 616956	0.6		0.806	0.838	0.868	0.913
Baldwin Farmer No 616914	0.6		0.811	0.850	0.872	0.923
Siemens Sondenfingerhutkammer No E28 U9 044	0.5		0.814	0.836	0.876	0.914
Siemens Sondenfingerhutkammer No E28 U11 067	0.5		0.815	0.841	0.875	0.917
Victoreen 100 R No 131	0.5		0.802	0.818	0.849	0.903
Victoreen 250 R No 154	0.2		0.806	0.824	0.848	0.887
Philips type 37498/10 No G 408 044	0.1		0.822	0.841	0.877	0.918
Philips type 37498/10 No G 408 002	0.1		0.820	0.845	0.885	0.917
		Mean value =	0.811	0.835	0.869	0.912
		SD =	0.007	0.010	0.012	0.011

* A small error in positioning the Philips 3 cm chamber has a large effect on the reading at low energy. The measurements at E = 8.5 MeV carried out with this large chamber are not included in the calculated mean value or standard deviation.

measurement point was between 50 and 500 rad/min depending on the electron energy. The liberated ionization expressed in e.s.u./cm^3 (at 20° C and 760 mm Hg) that is to be used in the calculations of recombination losses according to BOAG's theory (1956) was approximated by $M \cdot k_{60_{Co}} \cdot 273/293$. Theoretical values for general recombination were calculated and compared with experiment. In the experiments the chamber voltage U, was varied at a constant absorbed dose rate. A linear relationship existed between the ion current from the thimble chamber and the reciprocal collection voltage in accordance with LOEVINGER (1961). The collection efficiency was determined by extrapolation of the ion current against 1/U curve to infinite voltage. The measurements were carried out with positive and negative polarity of the collection voltage; the results were independent of polarity. The collection efficiency determined from experiment agreed with theory within 0.3 %.

$$E_m = E_o\left(1 - \frac{d}{R_p}\right)$$

where,

E_m indicates the mean energy of the primary electron at the depth, d (cm), in the water phantom, MeV

Measurements of absorbed dose in water, D_w. A detailed description of the ferrous sulphate dosimeter technique used in this laboratory was given by PETTERSSON & HETTINGER (1967).

Ferrous sulphate dosimeter solution in polystyrene irradiation cells was used for the determination of the absorbed dose in water, D_w. The irradiation cells were placed along the central ray in a water phantom (30 × 30 × 30 cm). The photometric measurements were carried out at 25.0 ± 0.2° C and the temperature during the irradiations was kept constant at 25 ± 1° C. A G value of 0.1556 $(eV)^{-1}$ (PETTERSSON 1967), and molar coefficient of 2.196 10^3 litre mol^{-1} cm^{-1} were used. The absorbed dose in water was estimated to be 0.4 % higher than in the dosimeter solution.

Exposure calibration, $k_{^{60}Co}$. Ionization chambers of type Victoreen and Baldwin Farmer were exposure calibrated at ^{60}Co γ radiation at the Swedish National Institute of Radiation Protection (in 1964, 1966 and 1967). The maximum systematic error of the obtained calibration factors was given as ± 3 %. The Baldwin Farmer chamber was also exposure calibrated at 2 MV at National Physical Laboratory (NPL), England, (in 1968). Systematic errors in the realization of the roentgen at 2 MV was unlikely to exceed 1 % in this laboratory (JENNINGS 1968). Exposure calibration factors obtained from the Swedish laboratory at ^{60}Co γ beam were 1.5 % lower than the values at 2 MV from NPL. The exposure calibration obtained from the Swedish National Institute of Radiation Protection was used to facilitate comparisons with earlier publications.

Thimble ionization chamber measurements, M. The measurements with the different ionization chambers in the water phantom were made without a build-up cap at the point of maximum absorbed dose along the central ray. A point 3/4 r in front of the chamber centre was considered as the measurement point, where r is the radius of the air cavity of the chamber (HETTINGER et coll. 1967, DUTREIX & DUTREIX 1966). The instrument reading, M, was corrected for general recombination (pulsed radiation), for temperature, and pressure.

Recombination losses were determined with the following methods. The betatron gives 50 radiation pulses per second, each 5 to 15 μ sec. The dose rate at the

Table 2

Scattering from the stem of the Victoreen 100 R chamber 5 cm of the stem was in the electron beam The increase of the Victoreen reading in per cent has been determined with and without a dummy stem in the beam

E_o/MeV	d/cm	E_m/MeV	Percentage increase
30 4	2 0	26 4	0 6
22 8	2 0	18 8	0 5
13 [illegible]	1 5	10 2	1 2
8 5	1 5	5 5	—0 7

and without a dummy stem placed in the radiation field 5 cm of the stem was in the radiation field (field size 8 × 10 cm) From Table 2 it appears that at the energies used here the ionization in the chamber cavity may be affected by up to 1 2 % depending on the scattering from the stem

Scattering within the air cavity HARDER (1968) pointed out that if a gas filled cavity is inserted into an electron irradiated liquid the fluence of electrons within the volume now occupied by the cavity is increased due to low scattering by the gas When the calculation method described is applied to the chambers in Table 1 the resulting increase in ionization will be greatest (about 2 %) for Philips 3 cm³ chamber at $E_m = 5\ 5$ MeV With Philips 0 1 cm³ chamber and $E_m = 26\ 4$ MeV (Table 1) the increase is a minimum about 0 2 %

Discussion and Conclusions

After application of corrections to the absorbed dose calibration factors (Table 1) for stem leakage stem scattering and scattering within the air cavity it has not been possible to show any systematic difference between the new corrected factors obtained for the different chambers These corrected factors are thus not confined to a specific type of thimble chamber and may be regarded as absorbed dose calibration factors for an ideal thimble ionization chamber Such factors are given in Fig 2 curve (b) These may be compared with theoretical D_w/J values (J = ionization in an air cavity at the measurement depth) SVENSSON (1971) made a comparison between k factors determined as above for an ideal thimble ionization chamber (E_m was between 4 and 40 MeV) and theoretical D_w/J from HARDER (1965b) BERGER & SELTZER (1969) and KESSARIS (to be published) and found agreement within 2 %

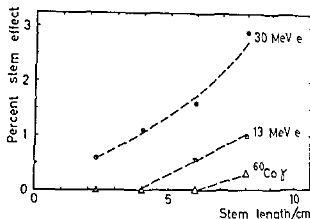


Fig. 1. Stem leakage effect of the Victoreen 100 R chamber at different radiation qualities: ^{60}Co gamma radiation and electrons with initial energies of 13 and 30 MeV.

Results

Table 1 summarizes the absorbed dose calibration factors. The mean k values of all the chambers at the different energies agree within 0.8 % with the results from SVENSSON & PETTERSSON (1967).

It appears that irrespective of chamber type absorbed dose calibration factors are obtained that vary maximally ± 2 % for a specific electron energy. To establish the reasons for the variations between different chambers correction factors other than pressure, temperature, and general recombination must be considered.

Influence of chamber construction

Stem irradiation. If great accuracy is desired the stem leakage effect must be investigated for different radiation qualities. In Fig. 1, one such measurement is represented, carried out with a Victoreen 100 R chamber for 13 and 30 MeV electron beams and for ^{60}Co γ radiation. The measurement technique did not allow the determination to include the effect of the part of the stem nearest the air cavity (≈ 1 cm). From Fig. 1 it can be seen that the stem effect is different for 30 and 13 MeV (about 1.5 % and 0.4 % increase of instrument reading with 5 cm irradiated stem respectively) and that no measurable effect is obtained with the ^{60}Co γ beam.

Scattering from the stem of the thimble chamber. Electron scattering in the stem can cause the electron fluence through the air cavity of the chamber to differ from that which would be obtained if the stem were to be replaced by water. This effect can be expected to be greatest with the Victoreen chamber since its stem is made from brass which has scattering properties very different from those of water. Measurements with the Victoreen 100 R chamber were carried out with

ZUSAMMENFASSUNG

Fur 6 Typen von kauflichen Fingerhut Ionisationskammern wurden die Kalibrierungs Faktoren fur die absorbierte Dosis im Punkte der maximalen absorbierten Dosis mit Elektronen strahlenenergien zwischen 8 und 30 MeV bestimmt Der Einfluss verschiedener Korrektions faktoren in Abhangigkeit von der Konstruktion der Kammer werden diskutiert Die Eigenschaften einer Fingerhut Ionisationskammer die fur Messungen der absorbierten Dosis in ho henergetischen Elektronenstrahlen geeignet ist werden zusammengefasst

RÉSUMÉ

Les auteurs ont determine les facteurs d etalonnage de la dose absorbee pour 6 types de chambres d ionisation de a coudre du commerce au point de dose absorbée maximale avec un faisceau d electrons dont l énergie allait de 8 a 30 MeV Ils ont analysé l influence de plusieurs facteurs de correction dependant de la construction de la chambre Ils decrivent brievement les propriétes d une chambre d ionisation de a coudre convenant pour la mesure de dose absorbee dans un faisceau d electrons de haute energie

REFERENCES

ALMOND P R The physical measurements of electron beams from 6 to 18 MeV Absorbed dose and energy calibration Phys in Med Biol 12 (1967) 13

— The use of ionization chambers for the absorbed dose calibration of high electron beam therapy units Int J appl Radiat (1970) 1

BERGER M J and SELTZER S M Quality of radiation in a water medium irradiated with high-energy electron beams Paper presented at the 12th International Congress of Radiology Tokyo Japan October 1969

BOAG J W Ionization chambers *In* Radiation dosimetry p 153 Edited by G J Hine and G L Brownell Academic Press Inc London 1956

DUTREIX J et DUTREIX A Etude comparée d une serie de chambres d ionisation dans des faisceaux d électrons de 20 et 10 MeV Biophysik 3 (1966) 249

HARDER D (a) Energiespektren schneller Elektronen in verschiedenen Tiefen *In* Symposium on high energy electrons p 26 Edited by A Zuppinger and G Poretti Springer Verlag Berlin 1965

— (b) Berechnung der Energiedosis aus Ionisationsmessungen bei Sekundarelektronen Gleichgewicht *In* Symposium on high energy electrons p 40 Edited by A Zuppinger and G Poretti Springer Verlag Berlin 1965

— Einfluss der Vielfachstreuung von Elektronen auf die Ionisation in gasgefullten Hohlraumen Biophysik 5 (1968) 157

HETTINGER G PETTERSSON C and SVENSSON H Displacement effect of thimble chambers exposed to a photon or electron beam from a betatron Acta radiol Ther Phys Biol 6 (1967) 61

HOSPITAL PHYSICISTS ASSOCIATION (HPA) A code of practice for the dosimetry of 2 to 35 MV X ray and caesium 137 and cobalt-60 gamma ray beams Phys in Med Biol 14 (1969) 1

INTERNATIONAL COMMISSION ON RADIATION UNITS AND MEASUREMENTS (ICRU) Report No 14 Radiation dosimetry X Rays and gamma rays with maximum photon energies between 0 6 and 50 MeV ICRU Washington 1969

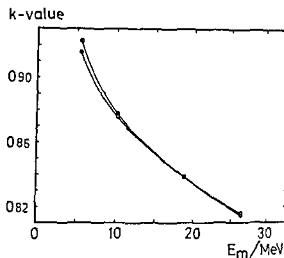


Fig 2 Absorbed dose calibration factors (k) are given in curve a (—○—) for a Siemens Sondenfingerhutkammer (connected to a Townsend compensation circuit) and in curve b (—□—) for an ideal thimble ionization chamber

Chambers with small values of the correction factors should be chosen for absorbed dose measurements since determination of the corrections are time consuming and systematic errors may occur Absorbed dose calibration factors for a Siemens Sondenfingerhut chamber, curve (a), (the same values are shown in Table 1) and for an ideal thimble ionization chamber, curve (b), are shown in Fig 2 The maximum difference between the curves is only 1 0 % The reason for this difference is almost exclusively dependent on the scattering in the air cavity calculated according to HARDER (1968)

SVENSSON (1971) showed for two particular chambers that for a given energy, E_m between 5 and 40 MeV the same absorbed dose calibration factors (within 2 %) are obtained with different betatrons It thus seems possible for centres without facilities for calorimetry or chemical dosimetry to use commercial thimble ionization chambers, exposure calibrated with ^{60}Co , radiation, for absorbed dose measurements of electron radiation

Acknowledgements

The work was supported by grants from the Swedish Cancer Society

SUMMARY

The absorbed dose calibration factors for 6 types of commercial thimble ionization chambers at the point of maximum absorbed dose were determined with electron beam energies between 8 and 30 MeV The influence of several correction factors dependent on the chamber construction were discussed The properties of a thimble ionization chamber suitable for absorbed dose measurements in high energy electron beams were summarized

FROM THE DEPARTMENT OF RADIOTHERAPY HALIFAX INFIRMARY HALIFAX NOVA SCOTIA CANADA

ERRORS IN THE DOSIMETRY OF ^{198}Au THERAPY

by

IBRAHIM B SYED

Radioactive gold has now completely replaced radon and long lived cobalt 60 or radium in mould and implant therapy because of the following advantages (1) avoidance of hospitalization or frequent visits of the patient, (2) protection of adjacent radio sensitive tissues (3) no recovery of the radioactive substances from moulds or implants is needed and (4) little radiation hazards to radiation and non radiation workers

The frequent use of ^{198}Au warrants careful estimation of the dose The current practice with regard to ^{198}Au therapy is either to apply the rules and tables of PATERSON & PARKER (1938) to find the number of mg h of radium required to deliver a certain dose to a specific area of tissue to convert the mg h into mCi of radon and then to the equivalent mCi of ^{198}Au or from the relation that 1 mCi of ^{198}Au after complete decay is equivalent to 28 30 mg h of radium Two errors are inherent in this procedure of dose estimation

The first error lies in the value of the specific gamma ray constant Γ for ^{198}Au used in the calculation of the equivalence of radon to ^{198}Au In standard textbooks the equivalence is given as

Part of this paper was presented at the Second International Conference on Medical Physics at Boston August 1969 Submitted for publication 4 August 1970

JENNINGS W A Personal communication (1968)
KESSARIS N D Absorbed dose and cavity ionization for high energy electron beams To be published in
LOEVINGER R Ionization chamber recombination loss in high intensity radiation fields *In* Selected topics in radiation dosimetry p 173 IAEA Vienna 1961
PETTERSSON C Calorimetric determination of the G value of the ferrous sulphate dosimeter with high energy electrons and ^{60}Co gamma rays Arkiv för Fysik 34 (1967) 385
— and HETTINGER G Dosimetry on high energy electron radiation based on the ferrous sulphate dosimeter Acta radiol Ther Phys Biol 6 (1967), 160
SVENSSON H Dosimetric measurements at the Nordic medical accelerators II Absorbed dose measurements Acta radiol Ther Phys Biol 10 (1971)
— and HETTINGER G Dosimetric measurements at the Nordic medical accelerators I Characteristics of the radiation beam Acta radiol Ther Phys Biol 10 (1971), 369
— and PETTERSSON C Absorbed dose calibration of thimble chambers with high energy electrons at different phantom depths *Arkiv för Fysik 34 (1967) 377*

Table 2

Comparison of physical parameters for Rn and Au

Radionuclide	Half life	Mean life	$\Gamma \frac{(R\ cm)}{mCi\ h}$
Rn	92 h	133 h	8 25
Au	65 h	93 6 h	2 34

Data from the decay scheme of ^{198}Au (see Figure) are taken to calculate the contributions of γ_1, γ_2 and γ_3 to the value of Γ (HAMILTON et coll 1962 STROMINGER et coll 1958)

The values for conversion coefficients α_K, α_L and α_{M+N} given by PARASIGNAULT (1966) for the 0 412 MeV gamma rays have been taken for the calculations as these values readily agree with those given in the NUCLEAR DATA SHEETS (1962) and by HAMILTON et coll 1965—66), DILLMAN (1969) and LEDERER et coll (1968)

For 0 412 MeV γ_1

α_t = 0 0426

α_K = 0 0283

α_L = 0 0111

α_{M+N} = 0 0031

where α_t is the total conversion coefficient

The calculations for determining the value of Γ for ^{198}Au are summarized in Table 3 The value obtained is 2 49 R cm /mCi h

$$1 \text{ mCi of radon destroyed} = \frac{8\,25 \times 133\text{ R}}{2\,49 \times 93\,6\text{ R}} = 4\,70 \text{ mCi of } ^{198}\text{Au after}$$

complete decay

For the Γ value of 2 49 R cm /mCi h 1 mCi of ^{198}Au after complete decay is equal to 28 30 mg h of radium equivalent where as for Γ value of 2 32 R cm /mCi h 1 mCi of ^{198}Au after complete decay is equal to 26 30 mg h of radium equivalent This affects the dosimetry of both permanent and removable implants If 1 mCi of ^{198}Au after complete decay is taken as 26 3 mg h radium equivalent then one is actually overestimating the dose by 8 0 % In other words if a dose of 6 000 rad is estimated to a permanent implant then the correct dose delivered will be 108 % of the estimated dose or 6 480 rad Then one can see that the lower Γ value for ^{198}Au results in overestimation of the dose by 8 0 % This is illustrated in Table 4

Table 1

The different values for the specific gamma ray constant Γ for ^{198}Au as given in the literature

$\Gamma \frac{(R\ cm^2)}{mCi\ h}$	Reference
2 19	GREENFIELD (1965)
2 27	WAGNER (1968)
2 3	SILVER (1968)
2 308	HENRY *(1969)*
2 34	JOHNS (1969)
2 35	HINE (1956)
2 40	HENSCHKE (1958)
2 42	SINCLAIR (1952)
2 43	A F C L
2 49	Present work

1 mCi of radon = 5 00 mCi of ^{198}Au = 26 6 mg h radium equivalent (JOHNS 1969)

One should remember that this equivalence is valid only when both radon and ^{198}Au decay completely In other words, the dose delivered at 1 cm by 1 mCi of radon, when it is left to decay completely is equal to the dose delivered at 1 cm by 5 0 mCi of ^{198}Au when the latter is also left for total decay

Different authors give different values for the equivalence This difference arises as already mentioned by using different values of Γ for ^{198}Au, these are summarized in Table 1 Hence, the literature is in complete disagreement regarding the value of Γ for ^{198}Au

From the data given in Table 2, one usually calculates the equivalence as follows

Total exposure dose at 1 cm from 1 mCi of a radioisotope after it decays completely equals Γ × average life In the case of radon it equals 8 25 × 133 R, and *in the case of* ^{198}Au 2 34 × 93 6 R

Therefore,

$$1 \text{ mCi of radon} = \frac{8\ 25 \times 133}{2\ 34 \times 93\ 6} = 5\ 00 \text{ mCi of } ^{198}\text{Au}$$

This equivalence is valid only when the *radioisotope decays completely*

Since the different values of Γ affect the equivalence of radon to ^{198}Au it was *decided to calculate the value of Γ for ^{198}Au from first principles* which are described elsewhere (LOEVINGER et coll 1956, SMITH 1965 SMITH et coll 1968)

Table 3

Calculation of Γ for ^{198}Au

Type of radiation	Photon energy E_i (MeV)	Fract. freq./disint. n_i	μ (air) cm	$\Gamma_i \frac{R\ cm}{mCi\ h}$
γ	0.412	0.956	3.82 × 10	2.26
Kα rtg ray	0.068	0.019	3.60 × 10	0.007
Kβ rtg ray	0.078	0.006	3.20 × 10	0.002
γ	0.676	0.010	3.80 × 10	0.041
γ	1.088	0.002	3.54 × 10	0.011
Bremsstrahlung	0.33	0.086	3.80 × 10	0.168
Total				2.49

Table 4

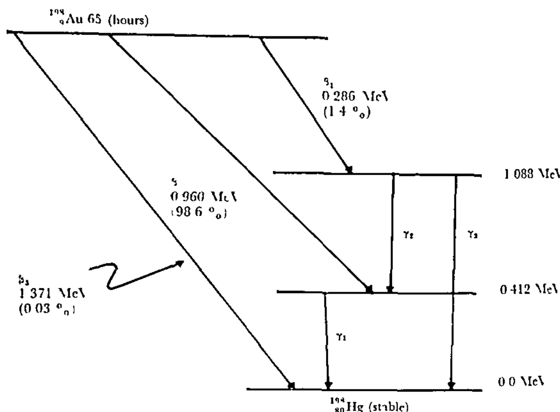
Variation in estimated dose using different values for Γ

$\Gamma \frac{(R\ cm)}{mCi\ h}$	$\frac{mCi\ Au}{mCi\ Rn}$ for complete decay	mg h (radium equivalent)	Dose estimate for 6000 rad: If Γ = 2.5 is true value	Dose estimate for 6000 rad: If Γ = 2.32 is true value
2.12	5.51	24.13	7000 rad	6500 rad
2.32	5.09	26.30	6500 rad	6000 rad
2.50	4.70	28.30	6000 rad	5500 rad

Table 5

The inverse variation of the percentage error of dose estimation with overall treatment time if correction is not made

Overall treatment time in days	Percentage error
5	28
6	21.5
7	16.5
8	13
9	10
10	8
12	4.8



Decay scheme of ^{198}Au γ_1 = 0.412 MeV (99.66 %) γ_2 = 0.676 MeV (1.06 %) γ_3 = 1.088 MeV (0.2 %)

The second error arises from the fact that dose estimation is affected if the treatment time is less or considerably less than the total decay time of ^{198}Au as in the case of moulds and removable implants. For practical purposes 30 days is taken as infinite time during which ^{198}Au decays completely.

The error can be illustrated by taking a hypothetical case in which an exposure of 6 000 R to a skin surface of 10 cm² is desired, using a mould at 0.5 cm treatment distance for 7 days. From the tables given by PATTERSON & PARKER one finds that 1 410 mg h is required to deliver 6 000 R. From other tables (MEREDITH 1958, WILSON 1948) one finds that 1 mCi of radon in 7 days has a cumulative dose of 95.51 mg h.

Hence the number of

$$\text{mCi of radon} = \frac{1\,410 \text{ mg h}}{95.51 \text{ mg h/mCi}} = 14.76$$

One may calculate the number of mCi of ^{198}Au required as equal to $14.76 \times 5.00 = 73.8$ mCi of ^{198}Au, whereas according to the present work $14.76 \times 4.7 = 69.4$ mCi of ^{198}Au are required.

Table 3

Calculation of Γ for Au

Type of radiation	Photon energy E_i (MeV)	Fract freq / disint n_i	μ (tr) cm	$\Gamma_i \frac{R\ cm}{mCi\ h}$
γ	0 412	0 956	3 82 × 10	2 26
Kα rtg ray	0 068	0 019	3 60 × 10	0 007
Kβ rtg y	0 078	0 006	3 20 × 10	0 002
γ	0 676	0 010	3 80 × 10	0 041
γ	1 088	0 002	3 54 × 10	0 011
Brems strahlung	0 33	0 086	3 80 × 10	0 168
Total				2 49

Table 4

Variation in estimated dose using different values for Γ

$\Gamma \frac{(R\ cm)}{mCi\ h}$	mCi Au / mCi Rn for complete decay	mg h (radium equivalent)	Dose estimate for 6000 rad: If Γ = 2 5 is true value	If Γ = 2 32 is true value
2 12	5 51	24 13	7000 rad	6500 rad
2 32	5 09	26 30	6500 rad	6000 rad
2 50	4 70	28 30	6000 rad	5500 rad

Table 5

The inverse variation of the percentage error of dose estimation with overall treatment time if correction is not made

Overall treatment time in days	Percentage error
5	28
6	21 5
7	16 5
8	13
9	10
10	8
12	4 8

This calculation is in error because the equivalence between radon and ^{198}Au does not hold good when the treatment time is short, about one week. As already pointed out, the equivalence is true only when the mould or implant is left till the complete disintegration of ^{198}Au or 30 days. In this case where the dose is to be *delivered in 7 days*, *the equivalent value of* ^{198}*Au in mCi* (4.70) should be multiplied by a factor of 0.86 which is the ratio of the percentage of radon decayed in 7 days to the percentage of ^{198}Au decayed in 7 days.

Hence, the correct number of mCi of ^{198}Au required will be $14.76 \times 4.7 \times 0.86 = 59.69$ *mCi of* ^{198}*Au*.

Thus, without the correction factor the calculation results in higher estimation of dose, an increase of 16.3 % or 6 978 R. This error varies inversely with treatment time as shown in Table 5.

The calculation to obtain the correct number of mCi of ^{198}Au can be cross-*checked to ensure the correct answer by the following two methods*.

(1) In 7 days 83.46 % of ^{198}Au decays completely. Out of the initial 59.69 mCi of ^{198}Au, after 7 days $59.69 \times 0.8346 = 49.82$ mCi of ^{198}Au should have decayed completely.

49.82 mCi of ^{198}Au is equivalent to 49.82/4.7 or 10.60 mCi of radon completely *decayed. Then the cumulative dose will be equal to* $10.60 \times 133 = 1\,410$ mg h radium equivalent.

This can also be verified as follows.

59.69 mCi in 7 days is equal to $59.69 \times 0.8346 = 49.82$ mCi of ^{198}Au decayed completely, which is equal to 49.82 mCi $\times$ 28.30 mg h/mCi = 1 410 *mg h equivalent*.

(2) The number of

$$\text{mCi of } ^{198}\text{Au required} = \frac{1\,410 \text{ mg h}}{28.3 \text{ mg h/mCi}} = 49.82$$

49.82 mCi of ^{198}Au in 7 days will deliver a cumulative dose equivalent to $49.82 \times 0.8346 \times 28.30$ *mg h radium* = *1 177 mg h* = 4 998 R, which is obviously incorrect.

Hence the correct number of

$$\text{mCi of } ^{198}\text{Au required} = \frac{1\,410 \text{ mg h}}{28.30 \times 0.8346 \text{ mg h/mCi}} = 59.69 \text{ mCi}$$

In order to simplify the calculations and avoid the error discussed in this paper Table 6 was prepared which directly gives the percentage decay of ^{198}Au in any *specific period of time and the corresponding* cumulative dose in mg h of radium equivalent without reference to radon which is useful in the estimation of the dose by the method of PATERSON & PARKER.

Table 6

Decay of Au and the equivalent dose in mg h radium equivalent

Days	Hours	Total number of hours	Percentage of Au decayed	Equivalent mg h per initial mCi of Au	
				Γ = 2 32	Γ = 2 49
	0	0	00 00	0 00	00 0
	1	1	1 07	0 28	0 30
	2	2	2 12	0 55	0 59
	3	3	3 16	0 84	0 89
	4	4	4 19	1 10	1 18
	5	5	5 21	1 37	1 47
	6	6	6 22	1 63	1 76
	7	7	7 22	1 89	2 04
	8	8	8 21	2 15	2 32
	9	9	9 19	2 40	2 59
	10	10	10 16	2 66	2 87
	11	11	11 11	2 94	3 17
	12	12	12 06	3 16	3 41
	13	13	13 00	3 40	3 67
	14	14	13 92	3 64	3 93
	15	15	14 84	3 89	4 20
	16	16	15 75	4 13	4 46
	17	17	16 65	4 37	4 71
	18	18	17 53	4 60	4 96
	19	19	18 41	4 81	5 19
	20	20	19 28	5 05	5 45
	21	21	20 14	5 29	5 71
	22	22	20 99	5 50	5 94
	23	23	21 83	5 70	6 15
1	0	24	22 67	5 94	6 41
	1	25	23 49	6 15	6 64
	2	26	24 30	6 35	6 85
	3	27	25 11	6 56	7 08
	4	28	25 91	6 77	7 31
	5	29	26 70	7 00	7 56
	6	30	27 48	7 20	7 77
	7	31	28 25	7 38	7 97
	8	32	29 01	7 58	8 18
	9	33	29 77	7 78	8 40
	10	34	30 52	8 01	8 65
	11	35	31 26	8 19	8 84
	12	36	31 99	8 36	9 02
	13	37	32 72	8 54	9 22
	14	38	33 43	8 74	9 43
	15	39	34 14	8 94	9 65

Table 6 *(cont.)*

Days	Hours	Total number of hours	Percentage of ^{198}Au decayed	Equivalent mg h per initial mCi of ^{198}Au	
				Γ = 2.32	Γ = 2.49
	16	40	34.84	9.13	9.86
	17	41	35.54	9.30	10.04
	18	42	36.22	9.48	10.23
	19	43	36.90	9.65	10.42
	20	44	37.58	9.85	10.63
	21	45	38.24	10.01	10.81
	22	46	38.90	10.18	10.99
	23	47	39.55	10.35	11.17
2	0	48	40.19	10.52	11.36
	1	49	40.83	10.69	11.54
	2	50	41.46	10.83	11.69
	3	51	42.08	11.03	11.91
	4	52	42.70	11.19	12.08
	6	54	43.92	11.53	12.45
	8	56	45.10	11.83	12.77
	10	58	46.27	12.14	13.11
	12	60	47.41	12.44	13.43
	14	62	48.52	12.71	13.72
	16	64	49.61	13.01	14.05
	18	66	50.68	13.29	14.35
	20	68	51.73	13.54	14.62
	22	70	52.75	13.80	14.90
3	0	72	53.75	14.08	15.20
	3	75	55.21	14.43	15.58
	6	78	56.63	14.85	16.03
	9	81	58.00	15.25	16.47
	12	84	59.33	15.57	16.81
	15	87	60.61	15.91	17.18
	18	90	61.86	16.23	17.52
	21	93	63.06	16.54	17.86
4	0	96	64.23	16.85	18.19
	3	99	65.36	17.17	18.54
	6	102	66.46	17.40	18.79
	9	105	67.52	17.66	19.07
	12	108	68.55	17.92	19.35
	15	111	69.54	18.18	19.63
	18	114	70.50	18.41	19.88
	21	117	71.44	18.69	20.18
5	0	120	72.34	18.94	20.45
	4	124	73.50	19.27	20.81
	8	128	74.61	19.5[illegible]	21.11

Table 6 (*cont*)

Days	Hour	Total number of hours	Percentage of ^{198}Au decayed	Equivalent mg h per initial mCi of ^{198}Au	
				Γ = 2 32	Γ = 2 49
	12	132	75 67	19 85	21 43
	16	136	76 69	20 08	21 68
	20	140	77 67	20 31	21 93
6	0	144	78 61	20 61	22 25
	4	148	79 51	20 87	22 53
	8	152	80 36	21 12	22 80
	12	156	81 19	21 32	23 02
	16	160	81 98	21 52	23 24
	20	164	82 73	21 70	23 43
7	0	168	83 46	21 88	23 62
	8	176	84 82	22 25	24 03
	16	184	86 06	22 56	24 36
8	0	192	87 21	22 87	24 69
	8	200	88 6	23 16	25 01
	16	208	89 22	23 41	25 28
9	0	216	90 11	23 62	25 50
10	0	240	92 35	24 20	26 13
12	0	288	95 42	25 04	27 03
14	0	336	97 25	25 48	27 51
16	0	384	98 36	25 87	27 93
18	0	432	99 02	26 00	28 00
20	0	480	99 41	26 15	28 14
25	0	600	99 94	26 17	28 16
30	0	720	99 96	26 19	28 18
∞	0	∞	100 00	26 30	28 30

The same problem can be solved using Table 6 in the following manner

In 7 days the cumulative dose per initial mCi of ^{198}Au is 23 62 mg h The number of mCi of ^{198}Au required for a cumulative dose of 1 410 mg h is given by

$$\frac{1\,410 \text{ mg h}}{23\,62 \text{ mg h/mCi}} = 59\,69 \text{ mCi of } ^{198}\text{Au}$$

Discussion

In this paper the values for $\mu_{n(al)t}$ used in Table 3 have been obtained by multiplying the mass energy absorption coefficients in air given by EVANS (1968) which are the best available with the density of air and by interpolation

These values can also be obtained from RADIOLOGICAL HEALTH HANDBOOK (1970) The value of Γ, obtained in the present work, which includes the contribution from bremsstrahlung is 2 49 R cm /mCi h

Acknowledgement

The author wishes to thank J F Filbee Director of the Department of Radiotherapy and W H Henry of the National Research Council of Canada for their useful suggestions and comments

SUMMARY

Two errors have been discussed in the dosimetry of ^{198}Au mould and implant therapy The first one which leads to an overestimation of the dose by 8% is due to the specific gamma ray constant Γ which has different values in the literature varying from 2 19 to 2 43 R cm /mCi h Hence the value of Γ for ^{198}Au was calculated from the first principles and found to be 2 49 R cm^2/mCi h which is different from the values given by the National Bureau of Standards (USA) and the National Research Council of Canada as they did not include the contribution from bremsstrahlung The second one which varies inversely with the treatment time arises from the equivalence of 1 mCi of radon to 5 0 mCi (4 70 mCi—present work) of ^{198}Au This equivalence is true only when both radon and ^{198}Au decay completely When treatment time is considerably short (1 week) as in the case of moulds and removable implants then the equivalent value of ^{198}Au in mCi should be multiplied by a factor which is the ratio of the percentage of radon decayed in one week to the percentage of ^{198}Au decayed in one week In order to simplify the calculations and avoid the above errors a table has been prepared which directly gives the percentage decay of ^{198}Au in any specific period of time and the corresponding cumulative dose in mg h of radium equivalent

ZUSAMMENFASSUNG

Zwei Fehler bei der Dosimetrie der ^{198}Au Form und Implantationstherapie werden besprochen Der erste der die Dosis um 8% zu hoch berechnet beruht auf der spezifischen Konstante Γ der Gamma Strahlung, fur die in der Literatur verschiedene Werte zwischen 2 19 und 2 34 R cm /mCi h angegeben sind Deshalb wurde der Wert von Γ fur ^{198}Au nach den ersten Grundsatzen bestimmt Es wurde ein Wert von 2 49 R cm /mCi h gefunden der sich von denen die das National Bureau of Standards (USA) und das National Research Council of Canada angegeben haben unterscheidet da diese nicht den Beitrag der Bremsstrahlung berucksichtigt haben Der zweite Fehler der sich umgekehrt mit der Behandlungszeit verandert ergibt sich aus dem Aquivalent von 1 mCi Radon zu 5 0 mCi (4 70 mCi in der vorliegenden Arbeit) ^{198}Au Dieses Aquivalent ist nur dann wirklich vorhanden wenn sowohl der Radon als auch der ^{198}Au Zerfall vollstandig ist Wenn die Behandlungszeit betrachtlich kurz ist (1 Woche) wie es der Fall bei Formen und entfernbaren Implantaten der Fall ist muss der Wert fur das Aquivalent von ^{198}Au in mCi mit

einem Faktor multipliziert werden der sich aus dem Verhaltnis des prozentuellen ^{198}Au Zerfalls einer Woche ergibt Um die Berechnungen zu erleichtern und um die obengenann ten Fehler zu vermeiden ist eine Tabelle herg stellt worden aus der sich der proz ntuelle Abfall von ^{198}Au fur j de spezifische Zeitperiode und die entsprechende kumulative Dosis in mg h des Radiumaquivalents ergibt

RÉSUMÉ

L auteur a etudie deux erreurs dans la dosimetrie de ^{198} Au utilis en moulage et en im plantation La premiere erreur qui surestime la dose de 8 % st due a la constante specifi qu de rayonnement gamma Γ qui a des valeurs differentes dans la litterature allant de 2 19 a 2 34 R cm /mCi h C est pourquoi la valeur de Γ pour ^{198}Au a ete calculee a par tir d s principes fondamentaux et trou ee egale a 2 49 R cm /mCi h de qui est different des valeurs donnees par le National Bureau of Standards (USA) et le National Research Coun il of Canada tant donne qu ils n ont pas inclu la contribution du rayonnement de freinage La seconde erreur qui varie en sens inverse de la duree du traitement provient de l equi alence de 1 mCi de radon a 5 0 mCi (4 70 mCi — travail de l auteur) de ^{198}Au Cette equivalence n est vraie que quand le Radon et ^{198}Au se desintegrent completement Qand le temps de trait ment est tres court (une semaine) comme dans le cas de moulage et d implant provisoire cette valeur equivalente de ^{198}Au en mCi devrait etre multipliee par un fa teur qui est le rapport du pourcentage de radon detruit en une emaine au pourcen tage de ^{198} Au detruit en une semaine Pour simplifier les calculs et pour eviter les erreurs mentionnees ci dessus l auteur a etabli une table qui donne directement le pourcentage de destruction de ^{198} Au dans les diverses periodes de temps et la dose cumulative correspon dante en mg h d equivalent de radium

REFERENCES

ATOMIC ENERGY OF CANADA LIMITED Commercial Products Division Decay tables for radioactive isotopes Technical Bulletin DK 4 (Gen 18)

DILLMAN L T Radionuclide decay schemes and nuclear parameters for use in radiation dose estimation MIRD Pamphlet 4 *J nucl Med* (*1969*) Suppl No 2 p 27

EVANS R D X ray and gamma ray interactions *In* Radiation dosimetry 2nd edition p 93 Edited by F H Attix and W C Roesch Academic press New York 1968

GREENFIELD M A Radioisotope dosimetry *In* Nuclear medicine p 93 Edited by W H Blahd McGraw Hill Book Company New York 1965

HAMILTON J H STOCKENDEL CAMP D C *et coll* The shape of the intense Au 198 beta sp ctrum and K conversion coefficient of the 412 keV J nu l Phys 36 (1962) 567

— — — Experimental values of internal conversion coefficients of nuclear transitions Nuclear Data Sec A 1 1 (1965) 521

HENRY W H Personal commun cation (1969)

HENSCHKE U K JAMES A G and MYERS W G The treatment of cancer with small sources of rad oactive gold *In* Treatment of cancer and allied diseases p 427 Edited by Pa k and Ariel Vol 1 Pitman Medical Publ shing Co London 1958

HINE G J Tables of data useful for dose calculation *In* Radiation dosimetry p 897 Ed ted by H J Hine and G L Brownell Academic Press N w York 1956

JOHNS H E and CUNNINGHAM J R The physics of radiology 3rd edition p 518 Charles C Thomas Springfield Illinois 1969
LEDERER C M Table of isotopes 6th edition p 119 John Wiley and Sons Inc New York 1968
LOEVINGER R, JAPHA E M and BROWNELL G L Discrete radioisotope sources *In* Radiation dosimetry p 694 Edited by G J Hine and G L Brownell Academic Press New York 1956
MEREDITH W J Radium Dosage The Manchester System E & S Livingston Ltd, London 1958
NUCLEAR DATA SHEETS N R C 5—2—55 (Dec 1962) Office of the Technical Services Washington 1956
PARSIGNAULT D The beta spectrum of Au 198 and the conversion coefficients of the 41? keV line in Hg 198 *In* Internal conversion processes, p 173 Edited by J H Hamilton Academic Press New York 1966
PATERSON R and PARKER H M A dosage system for interstitial radium therapy Brit J Radiol 11 (1938), 252 313
RADIOLOGICAL HEALTH HANDBOOK Compiled and edited by Bureau of Radiological Health USDHEW PHS Rockville 1970
SILVER S Radioactive nuclides in medicine and biology 3rd edition Lea & Febiger, Philadelphia 1968
SINCLAIR W K Artificial radioactive sources for interstitial therapy Brit J Radiol 25 (195?) 417
SMITH E M Internal dose calculations for Tc 99m J nucl Med 6 (1965) 231
— BROWNELL G L and ELLETT W H Radiation dosimetry *In* Principles of nuclear medicine p 742 Edited by H N Wagner JR W B Saunders Company Philadelphia 1968
STROMINGER D HOLLANDER J M and SEABORG G T The table of isotopes Rev Mod Phys *30 (1958)* 585
WAGNER JR H N Principles of nuclear medicine p 863 W B Saunders Company, Philadelphia 1968
WILSON C W Radium therapy Its Physical Aspects p 210 Chapman and Hall Ltd *London 1948*

MEASUREMENT OF RADIOACTIVITY IN BODY ORGANS

Report of a panel of experts of the International Atomic Energy Agency

When procedures with radionuclides require measurements of radioactivity in samples of blood urine tissue specimens etc in vitro the measurements are usually made under well defined physical conditions The main problems that then arise relate to statistical accuracy as a function of the sensitivity and background response of the detector Many procedures with radionuclides however also require measurements of radioactivity in body organs in vivo These measurements entail various additional problems which do not arise in measurements in vitro The measurement of radioactivity in an organ of irregular configuration and incompletely known position embedded in a medium that absorbs and scatters radiation involves many difficulties Other difficulties arise because of the complex and varying spatial distribution of radioactive materials within the human body and its organs

The report that follows was drawn up by a panel of experts convened by the International Atomic Energy Agency at its Headquarters in Vienna from 8 to 12 December 1969 to discuss the techniques available for the measurement of radioactivity in body organs The panel comprised Prof L DONATO (Italy) Dr P ESPINASSE (France) Dr H I GLASS (U K) Dr W J MACINTYRE (U S A) Dr J MYHILL (Australia) Dr W H OLDENDORF (U S A) Dr P TOTHILL (U K) Dr N VEALL (U K) and Dr R WOLF (Federal Republic of Germany) Dr E KOMAROV attended the meeting as representative of the World Health Organization Drs E H BELCHER R A DUDLEY and T NAGAI of the IAEA Secretariat also participated Dr Belcher acted as Scientific Secretary

General Considerations

Because of the limited range of β rays in the body tissues the measurement of radionuclides emitting only such radiation in body organs is possible only in a few special circumstances that are considered to be outside the scope of this report Almost all measurements of radioactivity in body organs are in fact measurements of radionuclides that emit γ or roentgen rays Most of the techniques at present used for such measurements are based on the use of non imaging fixed-detector systems the detectors being usually collimated so that they have appropriate directional properties Other techniques are based on whole body radioactivity determinations Still others are based on the analysis of data obtained in profile scanning procedures or in scintigraphic imaging procedures using either moving detector or fixed detector equipment It is clear that the choice of a technique for a given measurement depends on the type and accuracy of the information required It is beyond the scope of this report to detail all the possible techniques that can be used in measurements on a given organ (or region) of the body or to recommend specific techniques for each It does however provide a general review of the techniques at present available for such measurements and may lead to a better appreciation of the problems involved and how they can be overcome

Distribution of radioactivity within the body

Even when measurements are made with collimated detectors having directional properties it is usually impossible to detect radiation from the organ of interest to the complete exclusion of radiation from other regions of the body The radiation reaching the detector system may be regarded as the sum of the following components (1) Radiation due to radioactivity in the organ of interest and reaching the detector system either directly or after scattering (2) Radiation due to radioactivity in other regions of the body reaching the detector system either directly or after scattering, (3) Background radiation originating outside the body but modified as a result of the presence of the body as an absorbing and scattering medium

The measurement technique selected should clearly be one in which component (1) is detected with high efficiency whilst the contributions to the detector response due to (2) and (3) are as small as possible Even so corrections must usually still be made for the latter contributions In this connection it is relevant to point out that even when a collimated detector with a field of view conforming closely with the organ of interest is used radiation originating in tissues anterior or posterior to this organ may still contribute to the response Moreover when a collimated detector views an extended radiation source the fall in sensitivity with distance due to the inverse square law is counterbalanced by the increasing area of the field of view Tissues remote from the detector may thus make a considerably greater contribution than the collimator characteristics as measured with a point source might suggest

Distribution of radioactivity within the organ of interest

Radioactivity within the organ of interest is usually distributed among at least two if not more compartments which may be anatomic or physiologic sub divisions (BROWNELL et coll 1968) These include the circulating blood and various other extracellular and intracellular compartments The radioactivity in these different compartments usually varies with time in a different manner It is therefore necessary to determine which compartment is of primary interest select a suitable time (or times) for measurements and when necessary correct the measurements for contributions due to radioactivity in other compartments

Relative measurements

In view of the errors inherent in the calibration of in vivo radioactivity measurements in terms of measurements on a standard of known radioactive content it is preferable when possible to arrange matters so that such calibration is not necessary In many applications it is sufficient merely to relate measurements on the organ of interest to measurements on the same organ at some earlier or later time of reference as in ferrokinetic investigations with ^{59}Fe (HUFF et coll 1951) or radiocardiography with ^{131}I albumin (VEALL et coll 1954) Alternatively measurements may be related to simultaneous measurements over some other organ The latter may be the contralateral organ of the same type as in renography (TAPLIN et coll 1956) or a different organ as in the measurement of spleen/liver ratio in studies of sites of red cell destruction with ^{51}Cr (HUGHES JONES & SZUR 1957) These methods avoid many of the problems of calibration but still require an appreciation of the conditions of measurement, especially as regards absorption and scattering of radiation It must also be borne in mind that the relative contributions due to to radioactivity in compartments other than that of primary interest usually vary with time

In still other applications measurements on the organ of interest may be related to measurements on the same organ under conditions in which the radioactive material is administered by a different route or accumulated under different physiologic conditions An example of

such an application is given by the measurement of ventilation/perfusion ratio in different regions of the lung by means of radioactive gases administered alternatively by inhalation and by intravenous injection

Calibration methods

In many applications however calibration of the measurements is essential The most usual method of calibration is to relate the radioactive content of the organ of interest directly to that of the dose administered to the patient by comparing each measurement on the patient with a measurement on an external standard of known radioactive content contained in a phantom which simulates the organ concerned and its surrounding tissues the counting rate from the standard in the phantom giving the calibration factor

In a few instances it is possible to compare the initial measurement on the patient with a second measurement after the administration of an internal standard of known radioactive content given in such a form and by such a route that it is completely taken up by the organ concerned The increment in counting rate from the patient after administration of the internal standard then gives the calibration factor

Finally in a very few instances and with certain radionuclides coincidence counting techniques may permit the absolute measurement of radioactivity in the organ of interest without the need for either an external or an internal standard

Use of an external standard The external standard method requires accurate location and delimitation of the organ of interest and arrangement of the conditions of measurement so that radiation from all parts of the organ is recorded by the detector The standard and the phantom within which it is contained must simulate the organ of interest and its adjacent tissues as regards position size shape and ideally atomic composition How complete this simulation must be depends largely on the degree of uniformity of the sensitivity of the detector system to radiation originating from different parts of the organ

With a single collimated detector for which the sensitivity to a point source in an absorbing and scattering medium varies rapidly with the depth of the source the phantom must closely simulate the actual situation In particular the standard must be at the same depth in the phantom as is the organ of interest in the body tissues Uncertainty as to the depth of the organ may then be an important factor limiting the accuracy of the method

With multiple detector systems giving uniform sensitivity over a large volume the design of the phantom is less critical as long as the relevant attenuation of radiation is the same in the phantom and in the body tissues With a system consisting of two opposing detectors this requirement can be adequately satisfied by making the thickness of the phantom equivalent to the thickness of the body

A further factor limiting the accuracy of the external standard method whatever type of detector system is used is the presence of radioactivity in the tissues surrounding the organ of interest Such radioactivity contributes to the measurements on the patient but it is difficult to design the phantom so that measurements on it include a corresponding contribution

The external standard method is especially suitable for measurements on organs which are well-circumscribed superficial and easy to locate The classical example of its use is in the measurement of ^{131}I in the thyroid in the radioiodine uptake test of thyroid function International recommendations regarding the execution of such measurements have already been drawn up (IAEA 1961 1962 ICRU 1963) and a number of national and international intercomparisons in this field have been undertaken (BRUCER 1959 KAKEHI et coll 1964 MYHILL 1965 GOMEZ CRESPO & VETTER 1966) The method has also been used in the measurement

of ^{86}Rb in the heart in studies of myocardial blood flow (DONATO et coll 1966) and of ^{197}Hg in the kidneys in studies of renal function (RAYNAUD et coll 1968) It is difficult to apply however, in measurements on organs such as the liver pancreas spleen and stomach which are relatively large irregular in shape deeply situated and of uncertain position particularly when there is considerable radioactivity in the surrounding tissues (WOLF & FISCHER 1967)

Use of an internal standard In the internal standard method the standard is administered to the patient in such a form and by such a route that it is taken up specifically and completely or at least to a large and accurately known extent by the organ of interest The radionuclide of which the standard consists need not be identical with that which is to be measured but it must emit radiation of similar energy

As with the external standard method the presence of radioactivity in the tissues surrounding the organ of interest may limit the accuracy of the internal standard method However as long as the distribution of the original radioactivity and the internal standard within the organ of interest are similar the detector system need not record radiation from all parts of the organ Narrow collimation may thus be used to reduce the contribution from radioactivity in other regions of the body

Since in the internal standard method the patient serves as his own phantom this method is inherently more accurate than the external standard one However since each application of the method relies on a particular physiologic process it is not so generally applicable Examples of its use include the measurement of destruction of ^{51}Cr labelled red cells in the spleen using ^{51}Cr labelled damaged red cells as internal standard (SZUR et coll 1968) and the measurement of cerebral blood flow with ^{81}Kr^{m} using ^{85}Kr^{m} as internal standard (ARNOT et coll 1971)

A modification of this method has been utilized in the measurement of residual urine volume in the bladder using ^{131}I Hippuran (ROSENTHALL 1963) One hour after an intravenous injection of this tracer a measurement of the radioactivity in the bladder is made the patient is asked to void his bladder and the volume of urine passed is measured A second measurement of radioactivity in the organ is then made The decrement in counting rate after the patient has voided his bladder gives a calibration factor from which the residual urine volume can be determined

Absolute activity measurement With certain radionuclides which emit two or more photons (e g γ γ or γ X) in cascade coincidence counting techniques may be used to measure the absolute activity (disintegration rate) of an organ without the need for either an external or an internal standard The disadvantage of this method lies in its inherent low sensitivity which if a single detector system is used varies to a first approximation inversely as the fourth power of the source to detector distance This disadvantage can be minimized by using a large single detector or multiple detector system in close proximity to the organ Up to the present time the method has been applied only in the measurement of ^{125}I uptake by the thyroid (ESPINASSE & CHASTANIER 1969) It could however be used with other radionuclides emitting suitable radiations for example ^{111}In

Measurement techniques based on the use of fixed detector systems

Fixed detector systems for in vivo radioactivity measurements usually incorporate collimated thallium activated sodium iodide (NaI(Tl)) scintillation detectors The main problem encountered in the use of such systems is the reduction of unwanted contributions to the detector response due to radioactivity in regions of the body outside the organ of interest

Two methods are employed to reduce these unwanted contributions Firstly the detectors can be collimated so that their field of view covers no more than the organ and its immediate surroundings Secondly pulse height analysis can be used so that only pulses in the photo peak of the γ ray spectrum of the radionuclide concerned are recorded the contribution from scattered radiation is then largely excluded

It is important in this connection to distinguish the contribution due to radioactivity in tissues lateral to the organ of interest from that due to radioactivity in tissues anterior or posterior to it Collimation reduces the contribution due to radioactivity in lateral tissues but does not affect that due to radioactivity in tissues anterior or posterior to the organ Pulse height analysis improves the performance of the collimator by excluding the contribution from scattered radiation originating in lateral tissues as well as that originating in tissues anterior or posterior to the organ but at the cost of some sensitivity since it also excludes the contribution from scattered radiation originating in the organ itself

Physical expedients may thus reduce but cannot completely eliminate contributions due to radioactivity outside the organ of interest in particular a contribution due to radioactivity in tissues anterior or posterior to the organ usually remains In measurements on brain for example the overlying tissues may contain high levels of radioactivity (OLDENDORF & IISAKA 1969) Other unwanted contributions may arise from radioactivity in the circulating blood or other compartments within the organ itself Methods for correcting the measurements for these contributions include the following

Use of a shield One widely used method of correcting measurements of thyroid radioiodine uptake for extrathyroidal radioactivity is to repeat the measurement on the patient with a lead shield placed over the neck of the patient so as to cover the thyroid region (BRUCER 1959) The background thus measured on the patient is then subtracted from the initial measurement The lead shield in this method fulfils the role of the collimator in defining the field of view of the detector As in the use of a simple collimated detector however the method *does not correct for* the contribution due to radioactivity in tissues anterior or posterior to the thyroid It is important that the shield be thick enough to ensure that no radiation originating in the thyroid itself is recorded during the background measurement

The method has also been applied in measurements of radioactivity in the kidneys and liver in renal and hepatic clearance examinations with a whole body radioactivity measurement system (TROCZ et coll 1971)

Measurement over a neutral region A second method of correcting measurements of thyroid radioiodine uptake for extrathyroidal radioactivity is to repeat the measurement over another part of the body having similar dimensions to those of the neck—namely the thigh (MYANT et coll 1950 GOOLDEN & MALLARD 1958) The background thus measured is again subtracted from the initial measurement The method is open to the obvious criticism that the thigh is anatomically far from comparable to the neck it is however widely used (GOMEZ CRESPO & VETTER 1966)

Measurement at different times A third method of correcting measurements of thyroid radioiodine uptake for extrathyroidal radioactivity is to administer the dose of the radioisotope by injection and to make an initial measurement very shortly after the administration This initial measurement corresponds to a situation when most of the administered dose is extrathyroidal Corrections to subsequent measurements can then be derived from a consideration of the fraction of the dose taken up by the thyroid and the fraction excreted in the urine (ODDIE et coll 1955)

Use of blood radioactivity measurements It frequently happens that the unwanted contributions are due mainly to radioactivity in the circulating blood in the organ of interest and its surrounding tissues If the radioactive tracer used is one which is *injected intravenously and is cleared* relatively slowly from the circulation the initial measurement made on the organ corresponds to the situation when the whole of the administered dose is in the circulating blood Corrections for the contributions due to circulating blood radioactivity *at subsequent times can then* readily be derived from a curve of circulating blood radioactivity based on measurements of radioactivity in serial blood samples or in the heart This method has been applied in the measurement of radioactivity in the liver and *spleen in investigations of sites of red cell destruction* with ^{51}Cr labelled red cells (HUGHES JONES & SZUR 1957) and in the measurement of radioactivity in the bone marrow liver and spleen in investigations of iron metabolism with ^{59}Fe (HUFF et coll 1951) If the radioactive tracer used is *one which is cleared rapidly from the* circulation the appropriate factor to be used in making corrections for blood radioactivity may be determined by injecting a second more persistent tracer such as ^{131}I albumin a procedure which has been adopted in renography with ^{131}I Hippuran (HALL & MONKS 1966 BRITTON & BROWN 1968) and in the measurement of ^{86}Rb in the heart in studies of myocardial blood flow (DONATO et coll 1964) An alternative tracer that may be used for this purpose is ^{113}In^{m}, which *on intravenous injection in simple ionic form is rapidly and completely* bound by the plasma transferrin (HOSAIN et coll 1969)

Measurements with single collimated detectors

Detector systems incorporating a single collimated detector placed over the organ of interest have the obvious advantage of simplicity and are in fact widely used for measurements on many organs When a single detector is used however it must be accurately positioned so that the organ of interest lies within its field of view Moreover because of the combined effects of the inverse square law and attenuation of radiation in the body tissues its sensitivity to a point source of radiation falls rapidly with the depth of the source in the body tissues The effect of the inverse square law can to some extent be overcome by placing the detector further away from the body surface but only at the cost of reduced sensitivity and if the radioactivity in the organ of interest is low increased statistical errors in measurement The effect of attenuation becomes increasingly important at low photon energies thus the half thickness for ^{131}I γ rays (0 36 MeV) in soft tissue is 7 5 cm for ^{125}I roentgen rays (0 027 MeV) *only 2 2 cm If* therefore in measurements with a single collimated detector an external standard is to be used for calibration the effective depth of the organ in the body tissues must usually be established

Positioning of detector Methods for accurate positioning include the following

(1) Positioning from anatomic landmarks For many organs for example the brain heart liver lungs and thyroid this method is adequate though the possibility of displacement should always be considered with the heart and liver

(2) Positioning with reference to roentgenograms This method can be used for the heart and kidneys and for certain deeply situated organs such as the spleen and stomach With other deeply situated organs such as the pancreas however it is of little value Distortion on the roentgenogram can be reduced by using an increased tube distance The possibility of changes in position of organs with changes in posture should always be considered

(3) Positioning with reference to scintigrams This method may also be valuable for deeply situated organs The technique of transmission scintigraphy (KUHL et coll 1966) in which a

γ ray emitting source is placed behind the subject and the radiation transmitted through the body is recorded may be considered under this general heading

(4) Positioning at the point of maximum recorded counting rate This method is not necessarily a valid one but is often used for the kidneys in renography with ^{131}I Hippuran and may also be valuable for the bladder and thyroid It finds a particular application in tests for the location of the placenta

Depth of organ of interest Several methods are available for determining the depth of the organ of interest These include

(1) Measurement of the counting rates obtained with the detector at different distances from the body surface The resulting data may be analyzed in terms of the inverse square law or may be related to similar data obtained on phantoms These methods can be used only if contributions due to radioactivity outside the organ of interest but within the field of view of the detector are negligible They have been used to determine the effective depth of the thyroid in measurements of thyroid radioiodine uptake with ^{131}I (Myant et coll 1949 Schultz & Rollo 1970)

(2) Determination of the ratio of the counting rates obtained in two channels of the photon spectrum corresponding to the photo-peaks of two photons of different energies which are differently attenuated in the body tissues The photons in question may be derived either from the same radionuclide or from two radioisotopes of the same element administered simultaneously It is also possible to determine the depth of an organ from the ratio of the counting rates recorded in the photo-peak and in some part of the Compton continuum region of the photon spectrum due to a single photon These methods have the same limitation as those described in (1) above They have also been used to determine the effective depth of the thyroid in measurements of thyroid radioiodine uptake with ^{131}I alone (Wellman et coll 1967) and ^{125}I and ^{131}I in combination (Espinasse et coll 1969) They have been further used to determine the effective depth of the kidneys in renography with ^{125}I Hippuran and ^{131}I Hippuran in combination (Dolan & Tauxe 1968)

(3) Consideration of radiographic scintigraphic and other clinical evidence

If none of these methods are applicable the depth may be estimated from average anatomic data

Reduction of dependence of response on depth by spectrum subtraction method In certain circumstances in which the emitted radiation includes two photons of different energies the dependence of the sensitivity of the detector on the depth of the source in the body tissues may be reduced by a spectrum subtraction method which exploits the different attenuations of the two photons in the body tissues The method depends on measurement of the difference between the counting rates recorded in two channels of the photon spectrum corresponding to the two photons in question These photons may again be derived either from the same radionuclide or from two radioisotopes of the same element administered simultaneously Used in this way a single detector has a maximum sensitivity for sources at a finite depth depending on the energies of the photons in question so that the contribution of radioactivity in the superficial tissues to the total response is reduced

The method has been used in investigations of cerebral blood flow with ^{133}Xe the difference between the counting rates due to the 0 080 MeV γ rays and 0 030 MeV roentgen rays giving a maximum sensitivity at a depth of about 2 5 cm in soft tissue (Crawley & Veall 1970) The attenuation of the low-energy roentgen rays in the skull leads to a further separation of intra cranial from extracranial radioactivity (Oldendorf 1969) The method may prove useful with other radionuclides or mixtures of radioisotopes

Use of blood radioactivity measurements It frequently happens that the unwanted contributions are due mainly to radioactivity in the circulating blood in the organ of interest and its surrounding tissues If the radioactive tracer used is one which is injected intravenously and is cleared relatively slowly from the circulation the initial measurement made on the organ corresponds to the situation when the whole of the administered dose is in the circulating blood Corrections for the contributions due to circulating blood radioactivity at subsequent times can then readily be derived from a curve of circulating blood radioactivity based on measurements of radioactivity in serial blood samples or in the heart This method has been applied in the measurement of radioactivity in the liver and spleen in investigations of sites of red cell destruction with ^{51}Cr labelled red cells (Hughes Jones & Szur 1957) and in the measurement of radioactivity in the bone marrow liver and spleen in investigations of iron metabolism with ^{59}Fe (Huff et coll 1951) If the radioactive acer used is one which is cleared rapidly from the circulation the appropriate factor to be used in making corrections for blood radioactivity may be determined by injecting a second more persistent tracer such as ^{131}I albumin a procedure which has been adopted in renography with ^{131}I Hippuran (Hall & Monks 1966 Britton & Brown 1968) and in the measurement of ^{86}Rb in the heart in studies of myocardial blood flow (Donato et coll 1964) An alternative tracer that may be used for this purpose is $^{113}In^{m}$, which on intravenous injection in simple ionic form is rapidly and completely bound by the plasma transferrin (Hosain et coll 1969)

Measurements with single collimated detectors

Detector systems incorporating a single collimated detector placed over the organ of interest have the obvious advantage of simplicity and are in fact widely used for measurements on many organs When a single detector is used however it must be accurately positioned so that the organ of interest lies within its field of view Moreover because of the combined effects of the inverse square law and attenuation of radiation in the body tissues its sensitivity to a point source of radiation falls rapidly with the depth of the source in the body tissues The effect of the inverse square law can to some extent be overcome by placing the detector further away from the body surface but only at the cost of reduced sensitivity and if the radioactivity in the organ of interest is low increased statistical errors in measurement The effect of attenuation becomes increasingly important at low photon energies thus the half thickness for ^{131}I γ rays (0 36 MeV) in soft tissue is 7 5 cm for $^{1\ 5}I$ roentgen rays (0 027 MeV) only 2 2 cm If therefore in measurements with a single collimated detector an external standard is to be used for calibration the effective depth of the organ in the body tissues must usually be established

Positioning of detector Methods for accurate positioning include the following

(1) Positioning from anatomic landmarks For many organs for example the brain heart liver lungs and thyroid this method is adequate though the possiblility of displacement should always be considered with the heart and liver

(2) Positioning with reference to roentgenograms This method can be used for the heart and kidneys and for certain deeply situated organs such as the spleen and stomach With other deeply situated organs such as the pancreas however it is of little value Distortion on the roentgenogram can be reduced by using an increased tube distance The possibility of changes in position of organs with changes in posture should always be considered

(3) Positioning with reference to scintigrams This method may also be valuable for deeply situated organs The technique of transmission scintigraphy (Kuhl et coll 1966) in which a

In most clinical applications involving whole body radioactivity measurements the radioactivity administered to the patient itself serves as an internal standard and a measurement made on the patient shortly after its administration provides a calibration factor which can be used for all subsequent measurements If this approach is for any reason impracticable the measurement system may be calibrated by means of an external standard in a suitable phantom

A few days after administration of ^{131}I as iodide to a normal subj ct virtually all of the radio activity in the body is localized in the thyroid thyroidal ^{131}I uptake can thus be measured in terms of whole body radioactivity (LUSHBAUGH 1963) Such a technique is not normally to be r commended direct techniques based on the use of fixed detectors offer better sensitivity and better accuracy particularly in abnormal subjects in which the localization of ^{131}I in the thyroid is less complete The technique has proved valuable however in the detection of functional metastases in patients with thyroid carcinoma subjected to thyroidectomy (OBERHAUSEN 1966 ODDIE 1966)

Other examples of radioactive material which become almost exclusively localized in a sin le organ within a short time of their administration so that organ radioactivity may be measured in terms of whole body radioactivity include ^{4} Ca and ^{85}Sr which become localized in the skeleton and ^{57}Co ^{58}Co or ^{60}Co labelled vitamin B_1 which becomes localized in the l ver

Techniques based on the analysis of profile scanning data

In profile or linear scanning (POCHIN 1950) the distribution of radioactivity in one dimension in the body of the patient is determined in terms of the variations in counting rate recorded from a moving detector or system of detectors Counting rates may be recorded in analogue fashion by means of a ratemeter and strip-chart recorder or digitally the latter method facilitat i g subsequent analysis In certain circumstances the data thus obtained can be used to determine the radioactivity in specific organs or tissues

Profile scannin systems usually incorporate collimated NaI(Tl) scintillation detectors (CONCANNON & BOLHUIS 1957 MORRIS 1962 PIRCHER et coll 1962 ALFREY et coll 1967) Slit collimators mounted with their long axes perpendicular to the direction of motion of the detector are commonly used It may be advantageous to use detectors having long narrow crystals similarly mounted Cylindrical crystals can however be used end on and moving detector systems for whole body radioactivity measurement which usually incorporate detectors having such crystals can be easily fitted with collimator for profile scanning

The cho ce of collimator involves a comprom e between sensitivity and spatial resolution the provision of interchangeable or adjustable collimators is thus desirable to allow a choice appropriate to a given application For a profile scanning system with a single detector fitted with a s ngle slit collimator the re olution at a given depth of source is to a first approximation proportional to the aperture width whereas the sensitivity is proportional to the square of the aperture width

For the determination of rad oactivity in specific organs the variation of sensitivity with position of source within the body of the patient is of paramount importance With slit collimators the variation in sensitivity with position of source along a line parallel to the long axis of the collimator slit is usually quite small The sensitivity of a profile scanning system incorporating a single detector fitted with a single slit collimator falls rapidly however with depth of source The sensitivity of such a system towards sources in air varies inversely as the source to-detector distance (not as the square of this distance) In the body tissues the effect of attenuation is superimposed on this variation This makes quantitative results difficult to obtain

Measurements with multiple detectors

The dependence of response on depth of source which is characteristic of single collimated detectors may be to a large extent overcome by the use of systems comprising two or more detectors. Systems incorporating two opposing detectors connected in parallel provide a region midway between the detectors where sensitivity varies only slowly with position of source. With such systems the detectors can be placed close to the surface of the body with a consequent gain in sensitivity. Variations in response with depth of source due to the attenuation of radiation in the body tissues can be largely eliminated by calculating the geometric mean, arithmetic mean or some other combination of the counting rates from the two detectors.

Systems incorporating several detectors may offer geometric efficiencies approaching 100 %.

Dual detector systems with opposing detectors have been used in the measurement of ^{86}Rb in the heart in investigations of myocardial blood flow (DONATO et coll. 1966) and systems with obliquely disposed detectors in the measurement of ^{131}I uptake in the thyroid (WELLMAN et coll. 1967).

Other measurement techniques

While most measurements of radioactivity in body organs are carried out by techniques based on the use of fixed-detector systems, other techniques offer advantages in special situations. Techniques based on whole body radioactivity measurements or on the analysis of profile scanning data may be used when radioactivity is widely or irregularly dispersed throughout the body. Techniques based on the analysis of scintigraphic data may be used to measure radioactivity in large organs of irregular configuration. The main features of these techniques are discussed below.

Techniques based on whole body radioactivity measurements

In whole body radioactivity measurements (IAEA 1962, 1966) the total radioactivity in the body is determined regardless of its distribution among different organs and tissues. Such measurements can therefore be used to measure radioactivity in a body organ only when the radioactivity is exclusively localized in the organ in question or when the ratio of radioactivity in the organ to that in the whole body is known from other sources of information. Whole body radioactivity measurement is normally the method of choice for such purposes only for organs that are widely dispersed through the body.

Most whole body radioactivity measurement systems designed for clinical use incorporate NaI(Tl) scintillation detectors. A system in which one detector is positioned above and one below the patient, who lies on a couch which is caused to move longitudinally between the detectors, is particularly convenient for such purposes: whole body radioactivity is measured in terms of the cumulative count during a complete traverse of the patient. Sensitivity depends on crystal size and on the shielding provided, and can be made constant within a few per cent throughout the entire body of the patient by recording the count in a wide band of the photon spectrum (WARNER & OLIVER 1966, DUDLEY & BEN HAIM 1968). A not insignificant advantage of such a system is that it requires only the addition of collimators in order to be used for profile scanning.

Other systems used for clinical whole body radioactivity measurement incorporate large organic scintillation detectors which may almost completely surround the body of the patient. Such systems have the advantage of relatively high sensitivity, but are elaborate and expensive and cannot readily be modified to give information about the spatial distribution of radioactivity.

In most clinical applications involving whole body radioactivity measurements the radioactivity administered to the patient itself serves as an internal standard and a measurement made on the patient shortly after its administration provides a calibration factor which can be used for all subsequent measurements If this approach is for any reason impracticable the measurement system may be calibrated by means of an external standard in a suitable phantom

A few days after administration of ^{131}I as iodide to a normal subject virtually all of the radioactivity in the body is localized in the thyroid thyroidal ^{131}I uptake can thus be measured in terms of whole body radioactivity (LUSHBAUGH 1963) Such a technique is not normally to be recommended direct techniques based on the use of fixed detectors offer better sensitivity and better accuracy particularly in abnormal subjects in which the localization of ^{131}I in the thyroid is less complete The technique has proved valuable however in the detection of functional metastases in patients with thyroid carcinoma subjected to thyroidectomy (OBERHAUSEN 1966 ODDIE 1966)

Other examples of radioactive materials which become almost exclusively localized in a single organ within a short time of their administration so that organ radioactivity may be measured in terms of whole body radioactivity include ^{47}Ca and ^{85}Sr which become localized in the skeleton and ^{57}Co ^{58}Co or ^{60}Co labelled vitamin B_{12} which becomes localized in the liver

Techniques based on the analysis of profile scanning data

In profile or linear scanning (POCHIN 1950) the distribution of radioactivity in one dimension in the body of the patient is determined in terms of the variations in counting rate recorded from a moving detector or system of detectors Counting rates may be recorded in analogue fashion by means of a ratemeter and strip-chart recorder or digitally the latter method facilitating subsequent analysis In certain circumstances the data thus obtained can be used to determine the radioactivity in specific organs or tissues

Profile scanning systems usually incorporate collimated NaI(Tl) scintillation detectors (CONCANNON & BOITHUIS 1957 MORRIS 1962 PIRCHER et coll 1962 ALFREY et coll 1967) Slit collimators mounted with their long axes perpendicular to the direction of motion of the detector are commonly used It may be advantageous to use detectors having long narrow crystals similarly mounted Cylindrical crystals can however be used end on and moving detector systems for whole body radioactivity measurement which usually incorporate detectors having such crystals can be easily fitted with collimators for profile scanning

The choice of collimator involves a compromise between sensitivity and spatial resolution the provision of interchangeable or adjustable collimators is thus desirable to allow a choice appropriate to a given application For a profile scanning system with a single detector fitted with a single slit collimator the resolution at a given depth of source is to a first approximation proportional to the aperture width whereas the sensitivity is proportional to the square of the aperture width

For the determination of radioactivity in specific organs the variation of sensitivity with position of source within the body of the patient is of paramount importance With slit collimators the variation in sensitivity with position of source along a line parallel to the long axis of the collimator slit is usually quite small The sensitivity of a profile scanning system incorporating a single detector fitted with a single slit collimator falls rapidly however with depth of source The sensitivity of such a system towards source in air varies inversely as the source-to-detector distance (not as the square of this distance) In the body tissues the effect of attenuation is superimposed on this variation This makes quantitative results difficult to obtain

The use of a multi slit focused collimator may reduce the dependence of both the resolution and sensitivity of a single detector profile scanning system on depth of source. A more satisfactory solution to these problems, however, lies in the use of a system incorporating two opposing detectors, one on either side of the body of the patient. With such a system, if pulse height analysis is used to record pulses in the photo peak of the photon spectrum of the radionuclide concerned and if the counting rates from the two individual detectors are added, the sensitivity is found to be fairly uniform in the region midway between the two detectors. Calculation of the geometric mean of the two counting rates is found to give still better results (TOTHILL & GALT 1971). This finding applies in practice for both point and extended sources and for a wide range of photon energies.

Analysis of data. The analysis of profile scanning data involves the identification of the peak in the record corresponding to the organ of interest, the correction of the data for the effect of the finite resolution of the collimtor, for the effect of attenuation of radiation in the body tissues and for unwanted contributions due to radioactivity outside the organ of interest, and finally, the integration of the corrected counting rates over the peak in question.

Not the least difficulty in profile scanning arises in the identification of the various peaks in the record. The association of peaks with anatomic landmarks and observations on the variation of their intensity with time may both be helpful in this respect.

The finite resolution of the collimator distorts the relationship between the actual distribution of radioactivity and the scan record. In general, this distortion is of no consequence in the subsequent analysis and no corrections for it are needed. If necessary, corrections can be applied by computer methods.

Methods for correcting profile scanning data obtained with a single detector system for the effect of attenuation of radiation in the body tissues have been described (e.g. CORBETT et coll. 1956) but involve many difficulties. With a system incorporating two opposing detectors corrections for the effect of attenuation can more readily be made. For measurements on the abdomen, correction factors can readily be derived from measurements on an external standard in phantoms of various thicknesses. Attenuation in the thorax, however, varies markedly from point to point and calibration factors for measurements in this region are best derived from transmission measurements performed on the individual patient with external radiation sources (TOTHILL & GALT 1971). This method of calibration is necessarily approximate, but offers a practical alternative to the use of an anthropomorphic phantom completely matching the patient.

No general rules can be given for the correction of data for unwanted contributions due to base line radioactivity outside the organ of interest. In some cases, the base line for a particular peak can be derived directly from the record. In other cases, the variations in the record with time may be helpful. In still others, a second tracer labelled with the same radionuclide or emitting radiation of similar energy and known to be confined to the circulating blood or the extracellular compartment can be administered to the patient and used to determine the base line.

The collimation of a profile scanning system is usually designed so that the detector accepts radiation from the full width of the body. In certain cases, it may be advantageous to limit the acceptance to some section of the body, so as to confine attention to particular organs and reduce unwanted contributions from radioactivity elsewhere.

Profile scanning can be applied to the measurement of radioactivity in any transverse section of the body. Its application to the measurement of radioactivity in a particular organ does, however, depend on the absence of any concentration of radioactivity in other organs or tissues within the section of the body containing the organ in question, other than base line radio

activity for which a correction can be applied Thus it cannot separate radioactivity in the liver and spleen or the stomach and pancreas The method has been widely used to detect functional metastases in patients with thyroid carcinoma subjected to thyroidectomy and subsequently given therapeutic doses of ^{131}I It has also been used to study the distribution of labelled gases in the lung in investigations of regional ventilation and perfusion (WEST & DOLLERY 1960 DOLLERY & GILLAM 1963) Other applications include the measurement of uptake of $^{99}Tc^{m}$ by the thyroid as a test of thyroid function (FOTHILL & IRVINE 1967) the measurement of ^{59}Fe in various organs in studies of iron turnover (ALFREY et coll 1967) and the measurement of ^{131}I labelled thyroid hormones in the liver (POCHIN 1964)

Techniques based on the analysis of scinti raphic data

In scintigraphy a two-dimensional representation of the distribution of radioactivity in a chosen region of the body i obtained by means of either a moving-detector scanner or a fixed detector device such as a gamma-camera (IAEA 1964 1969) The data are usually displayed in analogue fashion as a pattern of dots or other marks on a sheet of paper or photographic film but may also be recorded digitally for subsequent analysis In the latter case it may be possible to derive quantitative information about the radioactivity in specific organs or tissues

Systems for quantitative scintig aphy Two important requirements in quantitative scintigraphy are that the sensitivity and resolution of the system (MACINTYRE et coll 1969) should be as far as possible independent of depth of source at least throughout the volume of the organ of interest

S ngle detector scanners and gamma-cameras satisfy these requirements only to a limited extent As regards sensitivity systems of both types approximate to infinite detectors provided that their field of detection is large compared with the projection of the organ of interest The inverse square law effect is therefore virtually absent but the dependence of sensitivity on depth of source due to attenuation of radiation in the body tissues remains Since most of the radionuclides used in scintigraphy emit low energy γ rays this effect is likely to be serious The resolution of a single-detector scanner is optimal in the focal plane of the collimator but worsens above or below this plane whil t that of a gamma-camera fitted with a multi hole grid collimator worsens continuously with source to-detector distance

These problems are largely avoided if a dual-detector scanner incorporating two opposing detectors is used By suitable choice of collimators the resolution of such a system can be held constant over a thickness of almost 30 cm (GENNA et coll 1969) As with profile scanning systems the s mple addition of the outputs of the two detectors gives a slow variation of sensitivity with depth whilst calculation of the geometric mean of the two counting rates may give better results (SHARMA 1968 ARIMIZU & MORRIS 1969 ARIMIZU et coll 1969 VAN STEKELENBURG & PALSMA 1970)

An assessment of the suitability of a system for quantitative scintigraphy requires a knowledge of the point source function of the coll mator-detector system at least to the 1 level for different depths of source in the body tissues This allows computation of the volume response of the system which is an important parameter in assessing the suitability of the system and its optimum operating conditions

Calibration is usually undertaken by the external standard method With single-detector scanners and gamma-cameras an independent estimate of effective organ depth is required and complex calibration procedures may be necessary With dual detector scanners calibration factors can be derived directly from simple measurements on standards in phantoms of

appropriate thicknesses Calibration factors must be measured for the appropriate size of standard thickness of phantom, scan speed and field size (WILLIAMS et coll 1969)

Analysis of data The analysis of the data must usually take into account not only the factors already mentioned but also the contributions due to radioactivity in tissues adjacent to the organ of interest and the *variations in response due to varying body thickness* With small organs such as the thyroid the work of analysis may be done manually but with larger organs computer processing is desirable A data acquisition system which accepts input counting rates up to at least 5×10^4 counts/s may be necessary

Contributions due to radioactivity in tissues adjacent to the organ of interest can be minimized by the use of appropriate collimation and pulse height analysis Corrections for such contributions must usually be made however and may be derived from measurements over the tissues in question or over a neutral region in which the concentration of radioactivity is similar Corrections for unwanted contributions due to radioactivity in the circulating blood can be derived from measurements with a second tracer which persists in the circulation If the image of the organ of interest overlaps that of a neighbouring organ the contribution due to radioactivity in the latter may similarly be derived from measurements over other regions of the neighbouring organ and from a knowledge of the degree of overlap The presence of a high level of radioactivity in neighbouring organs may however seriously interfere with the measurement of radioactivity in body organs by quantitative scintigraphy

Quantitative scintigraphy with a single detector scanner has been used to measure ^{131}I in the thyroid and in particular to study the question of extrathyroidal radioactivity in the thyroid ^{131}I uptake test of thyroid function (HILDITCH et coll 1967 TAUXE 1969) Both single detector and dual detector scanners have been used to measure the uptake of ^{99}Tc^m by the thyroid as a test of thyroid function (ANDROS et coll 1965 TOTHILL & IRVINE 1967 HARDEN et coll 1968 DE CARLETTA et coll 1968) Other applications of dual detector scanners include the measurement of ^{47}Ca in bone in calcium turnover studies (LAUGHLIN et coll 1969) and the measurement of ^{11}C carbon monoxide or ^{81}Rb in the spleen in studies of splenic blood volume and red cell destruction (GLASS et coll 1968 SZUR et coll 1968 WILLIAMS et coll 1969)

Relative sensitivities of different measurement techniques

Sensitivity is an important consideration in the choice of a technique for the measurement of radioactivity in a particular organ of the body Other things being equal it is always desirable to reduce the radiation dose to the subject and it may even be desirable to sacrifice some precision to achieve this aim

The sensitivity of a measurement technique depends primarily on the characteristics of the radionuclide to be measured on the geometric relationship between the organ of interest and the detector *on the efficiency of detection of radiation incident upon the detector* and on the radiation background the latter including the contribution due to radioactivity in other regions of the body With scanning systems several other factors must be taken into account *Firstly there is an inverse relationship in such systems between sensitivity and resolution* a collimator designed for good resolution has a poor sensitivity and vice versa Secondly the background in such systems is usually mainly due to radioactivity in other regions of the body Thirdly measurements with such systems must usually be extended well beyond the actual region of interest this leads to a reduction in the time available for measurements on the actual organ of interest

In view of these considerations only a general indication of the relative sensitivities of the

different measurement techniques described in this report can be given. Values of minimum measurable activity for the different techniques are given below.

Detector system	Minimum measurable activity (μCi)
Non-imaging fixed-detector system (single-detector)	0.1
Non-imaging fixed-detector system (multiple-detector)	0.01
Whole-body radioactivity measurement system (medium sensitivity)	0.1
Whole-body radioactivity measurement system (high sensitivity)	0.01
Profile scanning system (two opposing detectors)	0.1—1
Moving-detector scintigraphic system (small field), gamma-camera	1—10
Moving-detector scintigraphic system (large field)	10—100

The values given are estimates of the lowest activities which can be measured with reasonable precision and are about one order of magnitude greater than the corresponding minimum detectable activities. They relate to measurement times such as are commonly used in clinical investigations.

A limited number of sets of the working papers considered by the panel are available on request from the Medical Applications Section, International Atomic Energy Agency, P.O. Box 590, A-1011 Vienna, Austria.

SUMMARY

This report was drawn up by a panel of nine experts convened by the International Atomic Energy Agency in December 1969 to discuss the techniques available for the measurement of radioactivity in body organs. The report provides a general review of the techniques available for such measurements and the main problems which they entail. It deals in turn with measurement techniques based on the use of fixed-detector systems, techniques based on whole-body radioactivity measurements, *techniques* based on the analysis of profile scanning data and techniques based on the analysis of scintigraphic data. The present status of each technique is reviewed, its particular advantages and disadvantages are indicated and its main applications listed. Consideration is also given to the relative sensitivities of different techniques.

ZUSAMMENFASSUNG

Dieser Bericht wurde von einer Gruppe von neun Experten verfasst, die auf Einladung der Internationalen Atomenergie-Organisation im Dezember 1969 die zur Messung von Radioaktivität in Körperorganen zur Verfügung stehenden Methoden diskutierte. Der Bericht gibt eine allgemeine Übersicht der für solche Messungen anwendbaren Methoden sowie der damit

appropriate thicknesses Calibration factors must be measured for the appropriate size of standard thickness of phantom scan speed and field size (WILLIAMS et coll 1969)

Analysis of data The analysis of the data must usually take into account not only the factors already mentioned, but also the contributions due to radioactivity in tissues adjacent to the organ of interest and the variations in response due to varying body thickness With small organs such as the thyroid the work of analysis may be done manually but with larger organs computer processing is desirable A data acquisition system which accepts input counting rates up to at least 5×10^4 counts/s may be necessary

Contributions due to radioactivity in tissues adjacent to the organ of interest can be minimized by the use of appropriate collimation and pulse height analysis Corrections for such contributions must usually be made however and may be derived from measurements over the tissues in question or over a neutral region in which the concentration of radioactivity is similar Corrections for unwanted contributions due to radioactivity in the circulating blood can be derived from measurements with a second tracer which persists in the circulation If the image of the organ of interest overlaps that of a neighbouring organ the contribution due to radioactivity in the latter may similarly be derived from measurements over other regions of the neighbouring organ and from a knowledge of the degree of overlap The presence of a high level of radioactivity in neighbouring organs may however seriously interfere with the measurement of radioactivity in body organs by quantitative scintigraphy

Quantitative scintigraphy with a single detector scanner has been used to measure ^{131}I in the thyroid and in particular to study the question of extrathyroidal radioactivity in the thyroid ^{131}I uptake test of thyroid function (HILDITCH et coll 1967 TAUXE 1969) Both single detector and dual detector scanners have been used to measure the uptake of ^{99}Tc^{m} by the thyroid as a test of thyroid function (ANDROS et coll 1965 TOTHILL & IRVINE 1967 HARDEN et coll 1968 DE GARRETA et coll 1968) Other applications of dual detector scanners include the measurement of ^{47}Ca in bone in calcium turnover studies (LAUGHLIN et coll 1969) and the measurement of ^{11}C carbon monoxide or ^{81}Rb in the spleen in studies of splenic blood volume and red cell destruction (GLASS et coll 1968 SZUR et coll 1968 WILLIAMS et coll 1969)

Relative sensitivities of different measurement techniques

Sensitivity is an important consideration in the choice of a technique for the measurement of radioactivity in a particular organ of the body Other things being equal it is always desirable to reduce the radiation dose to the subject and it may even be desirable to sacrifice some precision *to achieve this aim*

The sensitivity of a measurement technique depends primarily on the characteristics of the radionuclide to be measured on the geometric relationship between the organ of interest and *the detector on the efficiency of detection of* radiation incident upon the detector and on the radiation background the latter including the contribution due to radioactivity in other regions of the body With scanning systems several other factors must be taken into account Firstly there is an inverse relationship in such systems between sensitivity and resolution a collimator designed for good resolution has a poor sensitivity and vice versa Secondly the background in such systems is usually mainly due to radioactivity in other regions of the body Thirdly measurements with such systems must usually be extended well beyond the actual region of interest this leads to a reduction in the time available for measurements on the actual organ of interest

In view of these considerations only a general indication of the relative sensitivities of the

CORBETT B D CUNNINGHAM R M HALNAN K E and POCHIN E E A profile counter and its calibration Phys in Med Biol 1 (1956) 37
CRAWLEY J C W and VEALL N The gamma pectrum subtraction technique for measurement of activity in body organs and its use for cerebral blood flow studies *In* Dynamic studies with radioisotopes in medicine p 585 IAEA Vienna 1971
DOLAN C T and TAUXE W N Estimation of organ depth by a double isotope technic Amer J clin Path 50 (1968) 83
DOLLERY C T and GILLAM P M S The distribution of blood and gas within the lungs measured by scanning after administration of xenon 133 Thorax 18 (1963) 316
DONATO L BARTOLOMEI G and GIORDANI R Evaluation of myocardial blood perfusion in man with radioactive potassium and rubidium and precordial counting Circulation 29 (1964) 195
— — FEDERIGHI G and TORREGGIANI G Measurement of coronary blood flow by external counting with radioactive rubidium Critical appraisal and validation of the method Circulation 33 (1966) 708
DUDLEY R A and BEN HAIM A Comparison of techniques for whole body counting of γ ray emitting nuclides with NaI(Tl) detectors I Point sources in phantoms II Distributed sources in phantoms and humans Phys in Med Biol 13 (1968) 181 194
ESPINASSE P et CHASTANIER P Une méthode de mesure absolue de l activite d une source d iode 125 Application a la mesure de la fixation thyroidienne de l iode 125 J Biol Med nucl 4 (1969) 16
— — and LAHNECHE B Thyroid uptake measurement using iodine 125 and iodine 131 Phys in Med Biol 14 (1969) 27
DE GARRETA A C GLASS H I and GOOLDEN A W G Measurement of the uptake of ^{99m}Tc by the thyroid Brit J Radiol 41 (1968) 896
GENNA S FARMELANT M H and BURROWS B A Improved scintiscan resolution without sensitivity loss Constant resolution collimator *In* Medical radioisotope scintigraphy I p 561 IAEA Vienna 1969
GLASS H I DE GARRETA A C LEWIS S M et coll Measurement of splenic red blood cell mas with radioactive carbon monoxide Lancet 1968 I p 669
GOMEZ CRESPO G and VETTER H The calibration and standardization of thyroid radioiodine uptake measurements A report on an IAEA project Int J appl Radiat 17 (1966) 531
GOOLDEN A W G and MALLARD J R A method for correction of extra thyroidal radioactivity Brit J Radiol 31 (1958) 41
HALL F M and MONKS G K The renogram A method of separating vascular and renal components Invest Radiol 1 (1966) 220
HARDEN R McG ALEXANDER W D SHIMMINS J and RUSSELL R I Quantitative uptake measurements of ^{99m}Tc in salivary glands and stomach and concentration of ^{99m}Tc ^{132}I and ^{8} Br in gastric juice and saliva *In* Radioaktive Isotope in Klinik und Forschung 8 Edited by K Fellinger and R Hofer Strahlentherapie Sonderband 67 (1968) 77
HILDITCH T E GILLESPIE F C SHIMMINS J et coll A study of extrathyroidal neck activity using a radioisotope scanner J nucl Med 8 (1967) 810
HOSAIN P HOSAIN F IQBAL Q M et coll Measurement of plasma volume using ^{99}Tc^{m} and ^{1} In^{m} labelled proteins Brit J Radiol 42 (1969) 627
HUFF R L ELMLINGER P J GARCIA J F et coll Ferrokinetics in normal persons and in patients having various erythropoietic disorders J clin Invest 30 (1951) 1512
HUGHES-JONES N C and SZUR L Determination of the sites of red-cell destruction using ^{51}Cr labelled cells Brit J Haemat 3 (1957) 320

verbundenen hauptsächlichen Probleme. Er befasst sich weiterhin mit Messmethoden für ortsfeste Detektorsysteme, Methoden, die Messungen der Ganzkörperradioaktivität zur Grundlage haben, Methoden, die auf der Analyse von aus Profilscanning gewonnenen Daten basieren, und Methoden, die auf der Analyse szintigraphischer Daten aufbauen. Der gegenwärtige Stand jeder dieser Methoden wird behandelt, ihre jeweiligen Vor- und Nachteile werden aufgezeigt und ihre Hauptanwendungsgebiete aufgezählt. Die relative Empfindlichkeit der verschiedenen Methoden wird ebenfalls behandelt.

RÉSUMÉ

Le présent rapport a été établi par un groupe d'étude comprenant neuf experts que l'Agence internationale de l'énergie atomique a, en décembre 1969, envoyé étudier les méthodes actuellement utilisées pour mesurer la radioactivité dans les organes du corps. Il présente un exposé général de ces méthodes et des principaux problèmes qu'elles soulèvent. Il étudie ensuite successivement les méthodes fondées sur l'emploi d'ensembles de mesure fixes, les méthodes fondées sur l'anthroporadiamétrie, les méthodes fondées sur l'analyse de données obtenues par des procédés de balayage du profil et les méthodes fondées sur l'analyse de données scintigraphiques. Le rapport indique quel est l'état actuel de développement de chacune de ces méthodes, quels sont ses avantages et inconvénients propres et donne la liste de ses principales applications. Il étudie aussi la sensibilité relative des différentes méthodes.

REFERENCES

ALFREY JR, C. P., COOK, V. and PITTMAN, J. P. The design and use of a linear scanner. J. nucl. Med. 8 (1967) 859.

ANDROS, G., HARPER, P. V., LATHROP, K. A. and McCARDLE, R. J. Technetium 99m pertechnetate localization in man with applications to thyroid scanning and study of thyroid physiology. J. clin. Endocr. 25 (1965) 1067.

ARIMIZU, N. and MORRIS JR, A. C. Quantitative measurement of radioactivity in internal organs by area scanning. J. nucl. Med. 10 (1969) 265.

— KAKEHI, H. and MORRIS JR, A. C. Area scanning for quantitative measurement of radioactivity in internal organs. In: Medical radioisotope scintigraphy 1, p. 653, IAEA, Vienna 1969.

ARNOT, R. N., GLASS, H. I., CLARK, J. C. et coll. Methods of measurement of cerebral blood flow in the newborn infant using cyclotron produced isotopes. In: Radioaktive Isotope in Klinik und Forschung 9. Edited by K. Fellinger and R. Hofer. Strahlentherapie Sonderband 70 (1971) 60.

BRITTON, K. E. and BROWN, N. J. G. The clinical use of C.A.B.B.S. renography. Investigation of the non-functioning kidney and renal artery stenosis by the use of ^{131}I Hippuran renography modified by computer assisted blood background subtraction (C.A.B.B.S.). Brit. J. Radiol. 41 (1968) 570.

BROWNELL, G. L., BERMAN, M. and ROBERTSON, J. S. Nomenclature for tracer kinetics. Int. J. appl. Radiat. 19 (1968) 249.

BRUCER, M. Thyroid radioiodine uptake measurement. A standard system for universal intercalibration. USAEC Rep. ORINS 19 (1959).

CONCANNON, J. P. and BOLHUIS, F. Studies with a modified collimator for use with scintillation counter for total body scanning. Amer. J. Roentgenol. 78 (1957) 855.

— Profile counting studies of hepatic uptake of labelled materials in man *In* Medical radio isotope scanning 2 p 447 IAEA Vienna 1964

RAYNAUD C DESGREZ A and KELLERSHOHN C Measurement of renal mercury uptake by external counting Separate functional testing of each kidney J Urol (Baltimore) 99 (1968) 248

ROSENTHALL L Residual urine determination by roentgenographic and isotope means Radiology 80 (1963) 454

SCHULZ A G and ROLLO F D A method for measuring radioiodine uptake which corrects for thyroid depth J nucl Med 11 (1970) 508

SHARMA R R Depth independence in quantitative radioisotope imaging Brit J Radiol 41 (1968) 949

VAN STEKELENBURG L H M and PALSMA D M H Quantitative measurement of radio activity J nucl Med 11 (1970) 179

SZUR L GLASS H I LEWIS S M et coll Quantitative estimation of red cell uptake in the spleen using ^{81}Rb- and ^{51}Cr labelled red cells Brit J Radiol 41 (1968) 819

TAPLIN G V MEREDITH O M KADE H and WINTER C C The radioisotope renogram An external test for individual kidney function and upper urinary tract patency J Lab clin Med 48 (1956) 886

TAUXE W N Estimation of thyroid uptake from digitized scintiscan matrices J nucl Med 10 (1969) 258

TKOCZ H J OBERHAUSEN E and GLOBEL B Measurement of liver clearance rate with partially shielded whole body counter *In* Dynamic studies with radioisotopes in medicine p 416 IAEA Vienna 1971

TOTHILL P and GALT J M Quantitative profile scanning for the measurement of organ radioactivity Phys in Med Biol 16 (1971) 625

— and IRVINE W J The use of technetium 99m for thyroid scanning and thyroid function testing *In* Radioaktive Isotope in Klinik und Forschung 7 Edited by K Fellinger and R Hofer Strahlentherap e Sonderband 65 (1967) 29

VEALL N PEARSON J D HANLEY T and LOWE A E A method for the determination of cardiac output (preliminary report) *In* Proc 2nd Radioisotope Conf Oxford p 183 Edited by J E Johnston Butterworths London 1954

WAGNER G T and OLIVER R A whole body counter utilizing the shadow shield technique Phys in Med Biol 11 (1966) 83

WELLMAN H N KEREIAKES J G YEAGER T B et coll A sensitive technique for measuring thyroidal uptake of ^{131}iodine J nucl Med 8 (1967) 86

WEST J B and DOLLERY C T Distribution of blood flow and ventilation perfusion ratio in the lung measured with radioactive CO_2 J appl Physiol 15 (1960) 405

WILLIAMS E D GLASS H I ARNOT R N and DE GARRETA A C A dual detector scanner for quantitative uptake and organ volume studies *In* Medical radioisotope scintigraphy 1 p 665 IAEA Vienna 1969

WOLF R und FISCHER J Untersuchungen am Phantom mit ^{51}Cr zur Frage der Beurteilung der Ergebnisse von Organaktivitatsmessungen Strahlentherapie 119 (1962) 276

IAEA Calibration and standardization of thyroid radioiodine uptake measurements Recommendations drawn up at a consultants meeting convened by the International Atomic Energy Agency Acta isotop (Padova) 1 (1961) 309, Minerva nucl 5 (1961) 4 Brit J Radiol 35 (1962) 205 Int J appl Radiat 13 (1962) 167 Acta ibér radiol-cancer 17 (1962) 183 Acta radiol 58 (1962) 731 J belge Radiol 45 (1962) 511

— Whole body counting IAEA Vienna 1962

— Medical radioisotope scanning 1 and 2 IAEA Vienna 1964

— Clinical uses of whole body counting IAEA *Vienna 1966*

— Medical radioisotope scintigraphy 1 and 2 IAEA Vienna 1969

ICRU Radioactivity Recommendations of the International Commission on Radiological Units and Measurements (1962) Rep 10c, US Dept of Commerce National Bureau of Standards Handbook 86 (1963)

Kakehi H Arimizu N Saegusa K and Watanabe I Japanese thyroid uptake survey Int J appl Radiat 15 (1964) 641

Kuhl D E Hale J and Eaton W L Transmission scanning A useful adjunct to conventional *emission scanning for accurately keying isotope deposition to radiographic anatomy* Radiology 87 (1966) 279

Laughlin J S Kenny P J Weber D A et coll Methods and applications of quantitative computer analysed scanning *In* Medical radioisotope scintigraphy 1 p 633 IAEA Vienna 1969

Lushbaugh C C A universally applicable *method* for assaying thyroid function in vertebrates Nature (Lond) 198 (1963) 862

MacIntyre W J Fedoruk S O Harris C C et coll Sensitivity and resolution in radio isotope scanning A report to *the* International Commission on Radiation *Units and* Measurements Nucl Med (Stuttg) 8 (1969) 99

Morris Jr A C A linear scanner for human radioisotope research US AEC Rep ORINS 33 (1960)

Myant N B Honour A J and Pochin E E The estimation of radioiodine in the thyroid gland of living subjects Clin Sci 8 (1949) 135

— Corbett B D Honour A J and Pochin E E Distribution of radioiodine in man Clin Sci 9 (1950) 405

Myhill J *The calibration of thyroidal uptakes in Australia* *Brit J Radiol* 38 (1965) 465

Oberhausen E Liquid scintillation whole body counters *In* Clinical uses of whole body counting p 3 IAEA Vienna 1966

Oddie T H Clinical applications of whole body radioiodine counting Ibid p 252

— Meschan I and Wortham J T Thyroid function assay with radioiodine 1 Physical basis of study of early phase of iodine metabolism and iodine uptake 2 Routine calculation of thyroidal and renal rate factors J clin Invest 34 (1955) 95 106

Oldendorf W H Utilization of characteristic X radiation to identify gamma radiation originating external to skull *J* nucl Med *10 (1969)* 740

— and Iisaka Y Interference of scalp and skull with external measurements of brain isotope content Part 1 Isotope content of scalp and skull Part 2 Absorption by skull of gamma radiation originating in the brain J nucl Med 10 (1969) 177 184

Pircher F J Brucer M Morris Jr A C and Black R The ORINS linear scanner in clinical diagnosis J nucl Med 3 (1962) 26

Pochin E E Investigation of thyroid function and disease with radioactive iodine I^{131} Lancet 1950 II pp 41 84

Use of risk estimates

The Commission discussed the use of risk estimates to assess the actual number of cases of disease that may be caused by any given exposure of individuals or of populations The Commission wishes to reiterate that its own recommendations are based upon the cautious assumption of linearity of effect with dose—even to the lowest levels—and that it considers this assumption prudent for planning the design and operation of sources leading to foreseeable conditions of exposure In these circumstances it may often suffice to assess what is considered to be an upper limit of hazard against which the benefit of a practice or the hazard of an alternative practice—not involving radiation exposure—may be based However the more cautious such a procedure is the more important it becomes to recognize that it may lead to an overestimate of the radiation risks which in turn could result in the choice of more hazardous alternatives to practices involving radiation exposures Thus in the choice of alternative practices radiation risk estimates should be used only with great caution and with explicit recognition of the possibility that the actual risk at low doses may be much lower than that implied by deliberately cautious assumptions

For a fuller discussion of this matter the reader is referred to ICRP Publication 8 and particularly to paras 1 1 to 1 4 of the Conclusions of that report

Exposure from intra oral roentgen tubes

The Commission was informed about a new radiation protection problem posed by the use of intra oral roentgen tubes in dental radiography With the present trend to use tubes of decreasing diameter the radiation doses at the surface of the tube may amount to between 50 and 100 rad or even more per exposure Such uses should be clearly deprecated It is of interest to note that intra oral roentgen tubes if used with the appropriate filtration and extra sensitive films may not give higher doses than 5—10 rad to limited parts of the tongue With these precautions the intra-oral tubes may even have certain advantages from the point of view of radiation protection they cause lower integral doses than regular dental tubes and the exposure of the staff is much reduced Extra shielding in the applicator can easily limit the radiation field to that which is needed for the examination thus further reducing the integral dose

Use of roentgen examination of airline passengers

The Commission has been asked for its views on an international proposal to use radiography as part of a system for the security screening of airline passengers This envisages that a small proportion of passengers might be examined radiographically using specially developed techniques that would restrict the exposure to 1 milliroentgen or less in any part of the body to be used only when other methods have indicated the presence of unexplained objects on the passenger Such passengers would be given the choice between a roentgen examination and a body search The Commission has already recommended that the irradiation of persons for non medical purposes such as in anti crime and customs examinations is generally to be deprecated However in view of the grave risks involved in the seizure of aircraft the Commission believes that the proposal if performed under the conditions already specified could be justified in the light of the benefits that might be expected

THE 1971 MEETING OF ICRP

The Commission and its committees met in London in April 1971 to review work being done and to plan future work. Three reports have been issued recently and are published by Pergamon Press; these are:

ICRP Publication 13	—	Radiation protection in schools for pupils up to the age of 18 years
ICRP Publication 15	—	Protection against ionizing radiation from external sources
ICRP Publication 16	—	Protection of the patient in X-ray diagnosis

Two more reports will be published in mid 1971. These are:

ICRP Publication 10a	—	Assessment of internal contamination resulting from recurrent or prolonged uptakes (a companion report to ICRP Publication 10)
ICRP Publication 17	—	Protection of the patient in radionuclide investigations

Publications 16 and 17, which deal with the protection of the patient, include information and guidance to all those who may influence — by administrative decisions, clinical judgement or technical handling of radiation sources — the radiation doses received by patients subject to medical examinations with roentgen rays or radioactive substances. Even though no maximum permissible levels are recommended for patients, these are not excluded from being subject to radiation protection. However, medical staff members are subject to the same maximum permissible levels as other radiation workers.

Population dose from consumer products

The Commission noted the increasing use of a number of consumer products containing small amounts of radioactive material, and the contribution to the population dose that these, taken together, could make, even though the dose from individual sources is at present extremely small. In considering the relevance of this to the dose limit for the population, the Commission emphasized the importance of national authorities assessing the contribution being made by these products, so that an effective means of control may be instituted. In this regard, the Commission wishes to draw attention to a publication of the European Nuclear Energy Agency (*Basic approach for safety analysis and control of products containing radionuclides and available to the general public. A guide prepared by an ENEA expert group*, ENEA, 1970) as an example of a method by which the total individual and population doses from all consumer products may be subject to administrative control.

ACTA RADIOLOGICA

OFFICIAL ORGAN OF THE RADIOLOGICAL SOCIETIES OF DENMARK, FINLAND NORWAY AND SWEDEN

Vol 10 Fasc 6 THERAPY PHYSICS BIOLOGY 1971 December

CONVENTIONAL AND SUPERFRACTIONATED RADIATION THERAPY IN BURKITT S LYMPHOMA

by

T NORIN P CLIFFORD J EINHORN NINA EINHORN B JOHANSSON G KLEIN J ONYANGO A DE SCHRYVER and R WALSTAM

Burkitt s lymphoma is the most common tumour found in children in certain parts of tropical Africa (WRIGHT 1967 BURKITT 1970 CLIFFORD 1971) The usual form of treatment at the present time is chemotherapy and the results published so far have been promising (CLIFFORD et coll 1967 COHEN et coll 1969 CLIFFORD 1970 1971 BURKITT 1970) Whereas there is extensive experience of the effect of chemotherapy in this disease reports on the results of radiation therapy are extremely sparse and apart from being most concerned with single cases they relate almost exclusively to patients outside the endemic Burkitt zones — presumably because there had been no resources for deep radiation therapy in such areas before 1968 The reported results of radiation therapy are at present limited to about a dozen patients in most of whom this form of treatment was combined with chemotherapy (ARAMSRI et coll 1967 BAI & AGRAWAL 1967 C D COLLINS et coll 1967 J M COLLINS et coll 1967 DELEMARRE et coll 1967 HALL & CUSSEN 1967 HOOGSTRATEN 1967 SAY

From the Departments of Radiotherapy and Head and Neck Surgery Kenyatta National Hospital Nairobi Kenya Radiumhemmet the Department of Tumour Biology and the Institute of Radiation Physics Karolinska Sjukhuset and Karolinska Institutet Stockholm Sweden

Submitted for publication 2 July 1971

Protection against non ionizing radiations

The Commission recognises that adequate control should be established over a number of sources of non ionizing radiation and notes that at present there is a need for international discussion about the biological criteria on which standards can be based However the Commission considers that this is a subject that lies outside its current field of work The Commission hopes that the issuing of this statement will facilitate and support moves to establish international action in this field The Commission intends to keep under review its own position in regard to the matter so as to ensure close co operation on a subject that has certain similarities with its own field of work

ACTA RADIOLOGICA

OFFICIAL ORGAN OF THE RADIOLOGICAL SOCIETIES OF
DENMARK, FINLAND NORWAY AND SWEDEN

Vol 10
Fasc 6

THERAPY PHYSICS BIOLOGY

1971
December

CONVENTIONAL AND SUPERFRACTIONATED RADIATION THERAPY IN BURKITT'S LYMPHOMA

by

T NORIN P CLIFFORD J EINHORN NINA EINHORN B JOHANSSON, G KLEIN
J ONYANGO A DE SCHRYVER and R WALSTAM

Burkitt s lymphoma is the most common tumour found in children in certain parts of tropical Africa (WRIGHT 1967 BURKITT 1970 CLIFFORD 1971) The usual form of treatment at the present time is chemotherapy and the re ults published o far have been promising (CLIFFORD et coll 1967 COHEN et coll 1969 CLIFFORD 1970 1971 BURKITT 1970) Whereas there is extensive ex perience of the effect of chemotherapy in this disease reports on the results of radiation therapy are extremely sparse and apart from being most concerned with ingle cases they relate almost exclusively to patients outside the endemic Burkitt zones — presumably because there had been no resources for deep radiation therapy in such areas before 1968 The reported results of radiation therapy are at present limited to about a dozen patients in most of whom this form of treatment was combined with chemotherapy (ARAMSRI et coll 1967 BAI & AGRAWAL 1967 C D COLLINS et coll 1967 J M COLLINS et coll 1967 DELEMARRE et coll 1967 HALL & CUSSEN 1967 HOOGSTRATEN 1967 SAY

From the Departments of Radiotherapy and Head and Neck Surgery Kenyatta National Hospital Nairobi Kenya Radiumhemmet the Department of Tumour Biology and the Institute of Radiation Physics Karolin ka Sjukhuset and Karolinska Institutet Stockholm Sweden Submitted for publication 2 July 1971



a b

A case of Burkitt s lymphoma (1226 M A Table 2) a) Before and b) 2 months after radiation therapy

et coll 1967, SHANMUGARATNAM et coll 1967, KRUCKEMEYER 1969, VOROBJEV et coll 1970) In some of these cases the tumours seem to have been radiation sensitive, and to have disappeared after application of doses of up to 3 000 rad (AHLSTROM et coll 1967) In others not even local control of the tumour was achieved within the irradiated area and there seems to be an appreciable risk of recurrence after radiation therapy

In December 1968, a radiation therapy department was started in Nairobi, Kenya (EINHORN et coll 1969) The early results obtained with radiation therapy in Burkitt's lymphoma in East Africa will be reported in this paper

In many cases of Burkitt s lymphoma chemotherapy has been beneficial but in some patients this form of treatment is not effective In the present series the decision to use radiation therapy was usually taken because the tumour had not responded to chemotherapy at that time In some cases irradiation was intended as a palliative measure and did not embrace all known locations of the tumour

Material The pre ent series compri es all the cases of Burkitt s lymphoma irradiated from December 1968 until October 1970 All but 2 were referred by and followed jointly with the Department of Head and Neck Surgery of the hospital the e 2 patients (1035 G G and 1266 M A) were referred by the Uganda Cancer Institute Kampala Uganda The case numbers refer to the Kenya Cancer Council (KCC) registration system

Of the 19 patients referred for radiation therapy 2 were excluded from the eries both these patients (984 O A 1124 O W) arrived at the hospital in extremely poor general condition and radiation therapy had to be di continued after one day

Of the remaining 17 patients 12 were boys and 5 girls their ages ranging from 3 to 12 years

In all cases the diagnosis was establi hed by hi tologic or cytologic examination of biopsy specimens taken before therapy

In these 17 patients the treatment was applied at 30 tumour sites

No of treated sites	1	2	3	5
No of patients	10	3	3	1

All patients were assigned to stages 3 A 3 B or 4 according to the staging described by CLIFFORD et coll (1967)

The tumour ites treated were

	No of tumour sites
Head and neck (mandibular maxillary orbital and parotid tumour)	15
Elsewhere in the skeleton	2
Brain and spinal cord	8
Abdomen (including kidney and spleen)	4
Testicle	1

In 4 patients radiation therapy was the initial form of treatment In 12 a tumour was progressing during chemotherapy and in one patient the treatment was given in combination with chemotherapy for this ca e the as essment of the effect of radiation therapy was considered as not reliable

Method The radiation ource was a cobalt unit (Siemens Gammatron) A FSD of 60 to 70 cm was u ed In all cases individual do e planning was performed all the do es reported are the calculated average tumour doses It is estimated that the target volume received this dose within limits of ± 15 per cent The treatment was applied on 5 or 6 days each week When radiation therapy was given on the indication of tumour cells in the cerebrospinal fluid the target volume covered the whole of the spine

Table I

Patients receiving radiation therapy by 1 (or 2) fractions a day

Case	Sex	Age years	Stage of tumour	Tumour sites	Total tumour dose rad	No of fractions	Period days	Dose/fraction, rad	No of treatments a day	Result*
1035 C C	M	9	3 A	Maxilla	5 100	25	30	205	1	(+)
				Fibula	3 600	8	9	450	1	(+)
952 M A	M	8	4	Maxilla	2 800	30	22	90	1 or 2	0
1009 J I	M	6	4	Eye	2 800	13	38	215	1	0
994 K M	F	7	4	Mandible	2 700	29	20	90	1 or 2	0
				Brain	2 600	21	35	125	1	0
976 M J	F	3	4	Mandible	2 500	20	28	125	1	(+)
					500	7	11	70	1	0
				Abdomen	200	6	11	30	1	0
849 N J	M	5	4	Testicle	1 900	8	8	210	1	+

* Scale of evaluation + complete or almost complete regression (+) moderate regression 0 no effect or else progress of irradiated tumour during therapy

Between December 1968 and December 1969, including the 'first period', 10 tumour sites were treated in 6 patients, all but 2 of the sites had one treatment per day Patient 952 M A received 30 fractions over 22 days given as 2 fractions on each of 11 days and one fraction on each of 8 days Patient 994 K M received 29 fractions on 20 days, given as 2 fractions on each of 11 days and one fraction on each of 7 days

In January 1970, the treatment schedule was changed and 3 treatments at intervals of 4 hours have been given each day, 5 days a week The daily number of treatments was thus consistently greater than in conventionally fractionated irradiation This technique is therefore referred to as superfractionated radiation therapy and the time from January 1970 referred to as the 'second period' During this period 20 tumour sites were treated in 11 patients

Evaluation of the results The observation time was 2 to 14 months after termination of radiation therapy The primary results were assessed one month after completion of the treatment Because of the short observation time only the early results of the therapy can be presented in this paper

The results have been assessed as follows (A) Disappearance of the tumour + (1) Palpable tumour regression until not palpable or hardly palpable (2) Non palpable tumour histologically or cytologically confirmed regression of the tumour refers usually to complete disappearance of previously abundant tumour cells in the cerebrospinal fluid (B) Moderate regression (+) (1) Palpable tumour regression but tumour still palpable (2) Non palpable tumours were always included in (A) or (C) groups (C) No effect 0 (1) Palpable tumour no regression or an increase in the size of the irradiated tumour during radiation therapy (2) Non palpable tumour histologically or cytologically demonstrable tumour cells on examination in vivo or post mortem

Results

At the tumour sites receiving doses of less than 1 000 rad no effect of the treatment was ever noted The e sites are therefore not further discussed in this account of the results they are included in Tables 1 and 2 but not in the summarizing Table 3

As a rule radiation therapy was well tolerated whether given with the conventional or with the superfractionation schedule This applies both to the general effects of radiation and to the local effect on non tumour tissue No consistent differences in the effect of irradiation on the numbers of white and red blood cells or platelets was observed between the 2 groups

There was no difference in the effect of irradiation between the patients where the tumour was resistant to the cytostatic therapy and the other cases

The areas treated were divided according to site the largest group including 14 sites were tumours localized to the head and neck region

Head and neck tumours (excluding the central nervous system)

First period (one treatment a day) Irradiation was given to 5 tumour sites in 5 patients (Table 1) The mean dose per fraction was 145 rad (range 90—215) and the mean total tumour dose was 3 200 rad (range 2 500—5 100) given over a mean period of 28 days (range 22—30) The mean number of fractions was 23 (range 13—30) In 2 of the patients there was a slight regression of the tumour and in 3 no effect (Tables 1 3)

Second period (3 treatments a day) Irradiation was given to 9 tumour sites in 6 patients (Table 2) Mean dose per fraction was 155 rad (range 120—185) mean total tumour dose 3 000 rad (range 2 200—4 000) over 8 days (range 4—10 days) Mean number of fractions was 19 (range 12—26) In all 9 of these treated sites there was complete regression but in one of them a rapidly growing recurrence appeared 5 weeks after termination of the treatment

Table 2

Patients receiving superfractionated radiation therapy by 3 fractions a day

Case	Sex	Age years	Stage	Tumour sites	Total tumour dose rad	No of fractions	Period days	Dose fraction rad	Result*	Remarks
1151 A A	F	7	4	Left kidney	4 100	28	14	145	0	
				Pelvic tumour	2 800	18	7	155	+	
				Lower thoracic and lumbar spine	1 900	12	4	160	+	
				Cervical and upper thoracic spine	1 900	12	6	160		
1003 J M	M	11	4	Mandible	4 000	26	10	150	+	
				Brain	2 400	34	15	70	0	
				Cervical cord	3 100	18	7	175		
				Thoracic spine	2 400	20	12	120	+	
				Lumbar spine	2 300	15	8	150		
				Left knee	2 400	14	7	170	not evaluable	
				Parotid gland	2 200	12	4	185	+	
1296 M A	F	12	4	Maxilla left	3 400	2[illegible]	9	160	+	
1229 O J	M	8	3 A	Mandible right	3 200	20	9	160	+	
1193 M M	M	8	3 A	Submandibular nodes	3 000	18	10	165	+	
				Maxilla right	2 800	18	8	155	+	
				left	2 800	18	7	155	+	Recurrence after 5 weeks
1154 M B	M	5	4	Maxilla	2 900	18	8	160	+	
				Spleen	800	6	1	130	not evaluable	
1064 J K	M	3	4	Brain	2 700	36	15	75	+	
1021 W W	M	7	4	Maxilla	2 600	22	9	120	+	
1080 W N	F	7	4	Brain	2 300	32	14	75	0	
117 O P E	M	8	4	Brain	2 900	40	21	70	not evaluable	Irradiation combined with chemotherapy
1046 W F	M	5	4	Brain	1 100	15	9	75	not evaluable	Died before treatment was finished

* For scale of evaluation see Table 1

Brain

First period In the only patient treated there was a slight subjective improvement but this was not reflected in the disappearance of tumour cells from the spinal fluid A total tumour dose of 2 600 rad was given in 21 fractions each of 125 rad over a period of 35 days (Tables 1, 3)

Second period Five patients were treated (Table 2) with a mean total tumour dose 2 300 rad (range 1 100—2 900) in 31 fractions each with a mean dose of 75 rad (range 70—75) over a mean period 15 days (range 9—21) (Table 3) In one of the patients in this group (1064 J K) there was complete clinical recovery and disappearance of tumour cells from the cerebrospinal fluid One of the patients died before the treatment was finished (1046 W F, Table 2) and in another radiation therapy was combined with chemotherapy (117 O P E Table 2) these 2 patients were regarded as not assessable (Table 3) In 2 cases the results of irradiation were recorded as negative (Table 3) in one (1080 W N Table 2) tumour cells were found in the cerebrospinal fluid one month after termination of irradiation the second (1003 J M Table 2) who presented with cranial nerve palsy with confusion had improved mentally and there was also regression of the paresis At post mortem examination 4 months after termination of irradiation no tumour involvement of the brain was found but massive tumour involvement of the trigeminal ganglion In accordance with the principles for evaluation of non palpable tumours this patient was recorded as deriving no effect from the treatment

Spinal cord

First period No patient

Second period Two patients were irradiated (Table 2) In both of them myelography before treatment revealed compression of the spinal cord The mean total tumour dose to the various areas of the spinal cord was 2 300 rad (range 1 900—3 100) Mean number of fractions was 16 (range 12—20) and mean dose per fraction 153 rad (range 120—175) over a mean period of 7 days (range 4—12) (Table 3)

In one patient (1003 J M Table 2) there were no lymphoma cells to be found in the cerebrospinal fluid at the in vivo examination after irradiation and the gross post mortem examination 4 months after treatment disclosed no signs of tumour However at histologic examination possibly a few lymphoma cells with signs of degeneration were found It was considered that there was a complete regression In the second case (1151 A A Table 2) post mortem examination 2 months after termination of irradiation revealed neither gross nor microscopic signs of tumour Complete regression was recorded

Table 3

Summary of the results of conventional (one treatment a day) and superfractionated (three treatments a day) radiation Patients receiving doses of more than 1000 rad

Conventional fractionation

Area treated	No of areas treated	Total dose rad		Dose/fraction rad		No of fractions		Period days		Results*		
		Mean	Range	Mean	Range	Mean	Range	Mean	Range	+	(+)	0
Head and neck	5	3 200	2 500—5 100	145	90—215	23	13—30	28	20—30	—	2	3
Brain	*1*	*2 600*	—	*125*	—	*21*	—	*35*	—	—	—	*1*
Spinal cord		—	—	—	—	—	—	—	—	—	—	—
Abdomen		—	—	—	—	—	—	—	—			
Testicle	1	1 900	—	240	—	8		8		1	—	—
Extremities	1	3 600		450		8		9		—	1	—

*For scale of evaluation see Table 1

Abdomen

First period Only one patient falls into this group, but the tumour dose did not exceed 1 000 rad (976 M J, Table 1)

Second period Only one patient with intra abdominal tumours received a tumour dose exceeding *1 000* rad The treatment was given on 2 occasions at 2 sites of the tumour A total tumour dose of 2 800 rad was given to a pelvic tumour and on a later occasion 4 100 rad to a tumour in one kidney (1151 A A, Table 2) The patient died of cerebral haemorrhage 2 months after termination of irradiation At post mortem examination tumour remnants were found in the kidney but neither gross nor microscopic examination revealed any signs of tumour in the pelvis

Extremities

First period One patient with a tumour of the fibula received 3 600 rad in 8 fractions each of 450 rad over 9 days (1035 G G Table 1) There was only slight regression of the tumour

Second period One patient with involvement of the left knee — verified as a radiologically demonstrated area of destruction — received 2 400 rad in 14

Table 3 (*cont*)

Superfractionated radiation therapy												
No of areas treated	Total dose rad		Dose/fraction rad		No of fractions		Period days		Results*			Not assessable
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	+	(+)	0	
9	3 000	2 200—4 000	155	120—185	20	12—26	8	4—10	9	—	—	—
5	2 300	1 100—2 900	75	70—75	31	15—40	15	9—21	1	—	2	2
2	2 300	1 900—3 100	153	120—175	16	12—20	7	4—12	2	—	—	—
2	3 500	2 800—4 100	150	145—155	23	18—28	11	7—14	1	—	1	—
	—	—	—	—	—	—	—	—				
1	2 400	—	170	—	14	—	5	—	—	—	—	1

fractions each of 170 rad over 7 days (Table 2) There was a subjective improvement but this was not confirmed by any histologic examination The result is therefore recorded as not assessable

Testicles

First period One patient with generalized Burkitt s lymphoma and a painful tumour in the testicle was treated with good results Over 8 days a total dose of 1 900 rad was given in 8 fractions each of 240 rad (849 N J Table 1) Post mortem examination disclosed no gross evidence of the tumour in the testicle

Discussion

Since Burkitt s lymphoma is a lymphomatous tumour with a histologic picture closely resembling that of lymphosarcoma (WRIGHT 1970) it would be expected to be highly radiation sensitive When the cobalt unit was installed in Nairobi at the end of 1968 and radiation therapy was started with doses that usually induce complete regression of a lymphosarcoma hardly any regression was recorded (Table 3) These disappointing results prompted a change in the

scheme of treatment. As Burkitt's lymphoma grows extremely rapidly, with a potential doubling time of less than 24 hours (COOPER et coll. 1966, 1968), the *number of fractions* was increased from one to 3 a day in order to increase the probability of hitting as many pre mitotic cells as possible. The radiation dose per fraction was kept largely unchanged and the total cumulative dose was about the same or somewhat lower than had previously been given with the conventional fractionation scheme involving one fraction a day. This change in fractionation technique led to a marked improvement in the results (Table 3).

The series reported here comprises all the patients with histologically confirmed Burkitt's lymphoma that received radiation therapy in Nairobi until October 1970, but of special interest in this connection are the patients in whom the results of the treatment could be assessed by palpation during and shortly after termination of irradiation — that is, mainly those with tumours in the head and neck and the testicles. In only one out of 6 such tumour sites treated by conventional fractionation was a satisfactory primary effect of the treatment obtained, whereas *in all 9 patients receiving superfractionated treatment an excellent effect* was recorded, and in none of them were definite tumour remnants found one month after treatment. From the results available so far it would seem unlikely that the observed differences in the local effect of the irradiation with these two fractionation schedules would change considerably over a longer follow up period. So far, there is evidence of local recurrence in only one of the patients in whom the tumour disappeared after irradiation.

The mean dose in 9 tumour sites in the head and neck region — all of whom reacted favourably to irradiation — was 3 000 rad, delivered in 19 fractions over 8 days (Table 3). The total doses were thus fairly high. A reduction might be possible with the superfractionation technique without impairing the favourable results. On the other hand it is not known whether the same effect could be obtained simply by further increasing the dose per fraction or the total radiation dose while retaining the schedule of one fraction a day. Whether enhancement of the biologic effect of the radiation on the tumour by superfractionation also will affect the non tumour tissues has not been established; the follow up time is too short to indicate whether the better effect on the tumour recorded with this fractionation scheme will be accompanied by a corresponding *potentiation* of the effect of the radiation on the healthy tissues.

In any case the effect of radiation therapy in Burkitt's lymphoma appears to be fairly capricious, and even with the same fractionation scheme 2 different doses can produce a different effect in a particular patient (1151 A. A., Table 2).

The superfractionation of the treatment in this particular series was initiated by the unexpectedly poor response of a lymphosarcoma like tumour to irradiation with conventional fractionation; this may have its explanation in the

unusually short generation time This type of fractionation was proposed by LITTBRAND & REVESZ (1969) on the basis of other radiobiologic considerations and actually tried in a few selected cases (JAKOBSSON et coll 1971) It has not been used consistently and it is possible that it can provide better results also in other malignant tumours than Burkitt s lymphoma Nor is it certain that the improvement in the results obtained in the present series has its explanation in the theoretical considerations that prompted the use of superfractionated therapy

It is still too early to assess the long term results of curative radiation therapy in Burkitt s lymphoma but it is noteworthy that the patient with the longest follow up (1064 J K Table 2) a case of cerebral involvement is still well 14 months after irradiation — which was the sole form of treatment — and without evidence of tumour cells in the cerebrospinal fluid

Acknowledgements

The authors would like to thank the Kenyan and the Swedish staff of the Department of Radiotherapy at the Kenyatta National Hospital Nairobi for their devoted work and Dr John Ziegler Uganda This project was supported by the Wallenberg Foundation the Bank of Sweden Tercentenary Fund the Kenya Cancer Council the British Empire Cancer Campaign for Research and the Einar och Lilly Gronberg s Foundation of Karolinska Sjukhuset

SUMMARY

In 17 cases of Burkitt s lymphoma 30 tumour sites were subjected to radiation therapy Doses up to 5 100 rad given in 25 fractions over 30 days with conventional fractionation (one treatment a day) yielded most disappointing results When a superfractionation schedule (3 *treatments a day*) was applied consistently better early results were obtained for the local effect on the tumours

ZUSAMMENFASSUNG

In 17 Fallen von Burkitt Lymphom wurden 30 Tumorstellen einer Strahlenbehandlung ausgesetzt Dosen bis zu 5100 *rad* die in 25 Fraktionen wahrend 30 Tagen mit konventioneller Fraktionierung (eine Behandlung taglich) gegeben wurden fuhrten zu vollstandig missgluckten Resultaten Wenn ein Superfraktionierungsschema (drei Behandlungen taglich) gegeben wurde wurden ubereinstimmend bessere fruhzeitige Resultate hinsichtlich des lokalen Effekts auf den Tumor erhalten

RÉSUMÉ

Dans 17 cas de lymphome de Burkitt 30 regions tumorales ont ete soumises a un traitement par les radiations Des doses allant jusqu a 5 100 rad administrees en 25 fractions sur 30 jours avec le fractionnement habituel (un traitement par jour) ont donne des resultats tres decevants Quand on a applique un schema de traitement superfractionne (3 seances par jour) on a obtenu de façon constante de meilleurs resultats precoces en ce qui concerne l effet local sur les tumeurs

REFERENCES

AHLQVIST J and WALLGREN G R *A case of Burkitt s lymphoma in Finland* Int J Cancer 2 (1967) 581

AHLSTROM C G, ANDERSSON T, KLEIN G and AKERMAN M Malignant lymphoma of Burkitt type in Sweden Int J Cancer 2 (1967) 583

ARAMSRI B, PINYARATN P KAMBHU P and THITATHAN S Burkitt s tumour in a Thai patient Int J Cancer 2 (1967) 586

BAI B M and AGRAWAL K L A case of Burkitt s lymphoma in India Int J Cancer 2 (1967) 588

BURKITT D P *General features and facial tumours In* Burkitt s lymphoma p 6 Edited by D P Burkitt and D H Wright E & S Livingstone Edinburgh and London 1970

— Treatment General features *In* Burkitt s lymphoma p 43 Edited by D P Burkitt and D H Wright E & S Livingstone Edinburgh and London 1970

CLIFFORD P Treatment Response to particular chemotherapeutic and other agents and treatment of CNS involvement *In* Burkitt s lymphoma p 52 Edited by D P Burkitt and D H Wright E & S Livingstone Edinburgh and London 1970

— Burkitt s lymphoma *In* Recent advances in radiotherapeutics and the treatment of *cancer Edited by H E Halman Churchill London 1971*

— SINGH S STJERNSWARD J and KLIN H Long term survival of patients with Burkitt s lymphoma an assessment of treatment and other factors which may relate to survival Cancer Res 27 (1967) 2578

COHEN M H BENNETT J M BERARD C W et coll Burkitt s tumour in the United States Cancer 23 (1969) 1259

COLLINS C D PULLAN J M TIGHE J R and VANIER T M A case of Burkitt s lymphoma in England Int J Cancer 2 (1967) 590

COLLINS J M BAKER H W HEINEMANN M W and MEIGHAN S S A case of Burkitt lymphoma in Oregon USA Int J Cancer 2 (1967) 592

COOPER E H FRANK G L and WRIGHT D H Cell proliferation in Burkitt s tumours Europ J Cancer 2 (1966) 377

— — — Cell proliferation in Burkitt s tumours *In* Cancer in Africa p 259 Edited by P Clifford C A Linsell and G L Timms East African Medical Journal/East African Publishing House Nairobi 1968

DELEMARRE J F M HOLLANDER C F FRENKEL M and DE LEEUW ISRAEL F R A case of a so called Burkitt tumor in a Dutch boy Int J Cancer 2 (1967) 594

EINHORN J EINHORN N and WALSTAM R Svenska radioterapiprojektet i Östafrika (In Swedish) Läkartidningen 66 (1969) 2493

HALL R K and CUSSEN L J Burkitt s tumour—an Australian case Int J Cancer 2 (1967) 599

HOOGSTRATEN J Observations on Burkitt s tumour in central and northern Canada Int J Cancer 2 (1967) 566

JAKOBSSON P Å LITTBRAND B and BACKSTROM A Ändrat fraktioneringsschema vid behandling av skivepitelcancer i munhåla (In Swedish) To be published in Nord Med

KRUCKEMEYER K Der Burkitt Tumor und sein strahlentherapeutischer Gestaltwandel Med Welt 20 (1969) 634

LITTBRAND B and REVÉSZ L *The effect of oxygen on cellular survival and recovery after* radiation Brit J Radiol 42 (1969) 914

SAY B HOSAL N and TINAZTEPE B A case of lymphosarcoma resembling Burkitt s tumor in a Turkish child Int J Cancer 2 (1967) 610
SHANMUGARATNAM K TAN K K and LEE K W Lymphoma of the Burkitt type in Singapore Int J Cancer 2 (1967) 576
VOROBJEV JU I A/RAHMAN EL SHEIKH EL TOM K H and HIDAYATALLA A The experience with radiation treatment of the Burkitt tumor (In Russian summary in English) Vop Onkol 16 (1970) 34
WRIGHT D H The epidemiology of Burkitt s tumour Cancer Res 27 (1967) 2424
— Microscopic feature histochemistry histogenesis and diagnosis *In* Burkitt s lymphoma p 82 Edited by D P Burkitt and D H Wright E & S Livingstone Edinburgh and London 1970

FROM THE DIVISION OF RADIOBIOLOGY, THE RESEARCH INSTITUTE OF NATIONAL DEFENCE, SUNDBYBERG, SWEDEN

DETERMINATION OF THE ^{131}I DOSE TO THE MOUSE THYROID

by

G WALINDER

The effects of radioiodine on thyroid glands are often presented in the literature as functions of the activities administered Investigations of this type presuppose that the dose to the thyroid is always proportional to the activities administered or, in other words, that the biologic and environmental parameters can be kept strictly constant and that the effects of the irradiation are not too extensive

The investigations of radiation effects on the mouse thyroid in progress aim at correlating the effects of high and low doses, and of different types of radiation, and of finding explanations of variations in the radiation damage as a function of age, environment etc It has thus been necessary to determine the radiation dose to the thyroid glands of the mice in every single experimental series

The present investigations were designed to form the general basis for the dose determinations by examining (1) the size of the thyroid, uptake and retention of ^{131}I as functions of age iodine content of the food, and diurnal

Submitted for publication 15 October 1970

Table 1

The relation between the 24 hour uptake and the iodine concentration in the diet

Type of food	Iodine concentration in the pellets μg/g (±SD)	24 hour uptake of the injected activity (±SE)	No. of animals
S diet	27 ± 3	2.4 ± 0.1	43
Ewos I	2.7 ± 0.5	7.3 ± 0.3	37
S I	1.0 ± 0.4	14.8 ± 0.6	20
Ewos II	0.74 ± 0.12	19.0 ± 1.7	20
Ewos III	0.33 ± 0.10	36.2 ± 0.7	72

and seasonal influence, (2) the dose distribution from ^{131}I accumulated in the thyroid gland by a film dosimetric method and comparing the results with the semitheoretic calculations of LOEVINGER et coll. (1956), and (3) the total integrated ^{131}I dose to the thyroid glands by a mathematical model based on (1) and (2).

Material and Methods

Animals and diet. All the test animals used were CBA mice born 20 to 21 days after conception and considered to be fully grown roughly 70 days after partus. (Mice are sexually mature at this age. A radical decrease in the metaphyseal osteoclasts in the 5th to 8th week of life is an indication that in the 70 day old mouse the immature skeletal growth has been completed (TONNA 1960).)

The animals were kept in thermostat regulated rooms with controlled humidity. The lights were automatically turned off at 6 p.m. and on at 6 a.m. The mice were always housed in groups of ten (or less) animals per cage. Normally the animals were maintained on a standard diet (S diet), which is designed to meet the ordinary protein, fat, carbohydrates, salt and vitamin requirements of the mouse. Tap water was supplied ad libitum. In addition to the standard diet four other types of food poor in iodine were used in the experiments. Three of these types were termed Ewos I, Ewos II and Ewos III (supplied by AB EWOS, Sodertalje, Sweden). The fourth type of pellets was made by the manufacturer of the S diet and called S I. The Ewos and S I pellets have the same composition as the S diet with the exception of the difference in the iodine content. The latter was determined by activation analysis at AB Atomenergi, Studsvik, Sweden (Table 1).

Determination of thyroid weights The weights of the thyroid gland in the full grown mice and all body weights were determined by weighing on a Sartorius analytical balance 2602 (precision ± 0 05 mg) The thyroids of the foetuses and young mice were too small to be weighed and the volumes of the glands were determined by making serial sections of the gland and measuring the area of the cut surfaces The thyroid glands from the foetuses were removed together with a piece of the trachea, and fixed in Susa's solution, treated with alcohol and xylol, according to conventional methods, and embedded in paraplast The tissue was then cut into sections, 21 μ thick, and stained with haematoxylin and eosin or with periodic acid Schiff (PAS) The fixation and staining of the tissue have been carried out according to ROMEIS (1948) The cut surfaces were measured in a microscope, fitted with an ocular micrometer, by dividing up the field of vision into bars, 32 μ thick, and adding up the areas of the bars over the thyroid The thickness of the sections was checked by weighing serial sectioned paraplast cylinders of known density

There is always a substantial shrinkage of the tissue involved in the fixation and drying procedures The ratio between the weights of seven newly excised thyroid glands of different sizes from adult mice and their volumes, as determined by analogy to those of foetal thyroids, was found to be 0 52 ± 0 02 It is assumed that this ratio is also valid for foetal thyroids

Uptake and retention of ^{131}I It was not possible to carry out reproducible measurements of the ^{131}I content in the thyroid gland in vivo mainly because the submaxillary gland of the CBA mouse covers the thyroid and in itself absorbs not inconsiderable amounts of iodine For determination of the activity in the thyroid, the glands were removed, hydrolyzed in 1 ml conc NaOH solution, and measured for activity in a well type crystal connected to a two channel scaler (Picker Twinscaler II)

Film dosimetry All the dose measurements were performed with photographic film (Eastman Kodak Cine Positive 5302) This film was chosen mainly because of the extreme thinness of the AgBr layer (0 72 mg cm) and the fine granules of the film emulsion which only to a negligible degree disturbed the absorption and scattering of the beta radiation in the otherwise relatively tissue equivalent material The film is linearly dose dependent up to a blackening of 2 0, read off in the microphotometer used for the experiments All the exposure times were chosen so that linear dose blackening relations would be obtained The film has been investigated and discussed from the dosimetric standpoint in earlier publications (WALINDER 1957 NOTTER & WALINDER 1959)

The thyroid glands of adult animals for the dosimetry investigations were removed 24 hours after an injection of ^{131}I (carrier free Na ^{131}I from the

Radiochemical Centre Amersham England) For the corresponding examina ion of foetal neonatal thyroids newborn animals were killed two days after ntravenous injections of ^{131}I to the mothers (on the 18th day of gestation)

The do e measurements were ba ed on the following principles If a thyroid obe containing a radioactive substance is ectioned down to the plane of sym netry a point on the cut urface will receive half the dose which the same point would have received in an intact gland lobe This is provided that the dose distri bution in the tissue is fairly homogeneous and that the part of the gland that has been cut away is replaced by an inactive material with an equivalent back cat tering capacity The shrinkage involved in the conventional fixation and drying procedures made it necessary to use a different technique when preparing the ti ue

The thyroid lobe of adult animals was quickly removed and separated from the trachea The lobe was transferred to a small air tight plastic box and then weighed and measured for activity After these measurements the lobe was placed on a small cube of ice covered with a thin layer of 0 9 % NaCl solution o that its longitudinal axis coincided with the surface of the saline made possible by adjusting the olution to reach half way up the lobe The little quare box containing ice cube NaCl solution and thyroid lobe was then sunk into a small beaker surrounded by solid carbon dioxide and acetone Following the freezing process that part of the thyroid lobe which lay above the frozen NaCl solution was removed by frozen sectioning down to the surface of the ice cube (and thus to the symmetry plane of the gland) The thyroids in newborn mice were not removed the whole neck region was frozen in the solid carbon dioxide acetone mixture The neck was then cut down sagittally by frozen ectioning until one of the lobes was inter ected The film was mounted on a thick Mix D disc (an infinite β reflector) and placed together with a film press in a box containing silica gel The box was then left to tand in the cold for a few of hours at a temperature of —20° C The formation of frost on film and press was thus avoided (Mix D is a tissue equivalent mixture prepared by JONES & RAINE (1949) consisting of 60 8 % paraffin wax 30 4 % polythene 6 4 % MgO and 2 4 % TiO_2)

In order to ensure that any olid carbon dioxide remaining on the cut urface would evaporate the ice cube (or the neck) containing the frozen gland tis ue was left to stand for a few hours in the refrigerating room in the above mentioned box to become acclimatized before the film was pressed against the cut surface After an exposure of 1 to 2 days the film was developed and fixed at the ame time and in the same bath as a calibrated film The blackening in different parts of the exposed film surface was read in a microphotometer Schnell photometer G II C Zeiss Jena Germany) The relations between

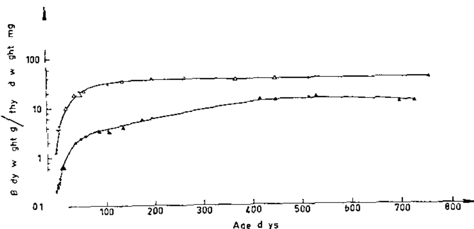
Determination of thyroid weights The weights of the thyroid gland in the full grown mice and all body weights were determined by weighing on a Sartorius analytical balance 2602 (precision ± 0 05 mg) The thyroids of the foetuses and young mice were too small to be weighed and the volumes of the glands were determined by making serial sections of the gland and measuring the area of the cut surfaces The thyroid glands from the foetuses were removed together with a piece of the trachea, and fixed in Steve s solution, treated with alcohol and xylol, according to conventional methods, and em bedded in paraplast The tissue was then cut into sections, 21 μ thick, and stained with haematoxylin and eosin or with periodic acid Schiff (PAS) The fixation and staining of the tissue have been carried out according to ROMEIS (1948) The cut surfaces were measured in a microscope, fitted with an ocular micrometer, by dividing up the field of vision into bars, 32 μ thick, and adding up the areas of the bars over the thyroid The thickness of the sections was checked by weighing serial sectioned paraplast cylinders of known density

There is always a substantial shrinkage of the tissue involved in the fixation and drying procedures The ratio between the weights of seven newly excised thyroid glands of different sizes from adult mice and their volumes, as deter mined by analogy to those of foetal thyroids, was found to be 0 52 ± 0 02 It is assumed that this ratio is also valid for foetal thyroids

Uptake and retention of ^{131}I It was not possible to carry out reproducible measurements of the ^{131}I content in the thyroid gland in vivo, mainly because the submaxillary gland of the CBA mouse covers the thyroid and in itself absorbs not inconsiderable amounts of iodine For determination of the activity in the thyroid, the glands were removed, hydrolyzed in 1 ml conc NaOH solution, and measured for activity in a well type crystal connected to a two channel scaler (Picker Twinscaler II)

Film dosimetry All the dose measurements were performed with photographic film (Eastman Kodak Cine Positive 5302) This film was chosen mainly because of the extreme thinness of the AgBr layer (0 72 mg cm) and the fine granules of the film emulsion, which only to a negligible degree disturbed the absorption and scattering of the beta radiation in the otherwise relatively tissue equivalent material The film is linearly dose dependent up to a blackening of 2 0, read off in the *microphotometer used for the experiments* All the exposure times were chosen so that linear dose blackening relations would be obtained The film has been investigated and discussed from the dosimetric standpoint in earlier publications (WALINDER 1957, *NOTTEP & WALINDER 1959*)

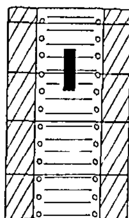
The thyroid glands of adult animals for the dosimetry investigations were removed 24 hours after an injection of ^{131}I (carrier free Na ^{131}I from the



F g ? Body and thyro d weights in relation to age in male CBA mouse White triangles indicate body we ght and solid triangles th roid eight. The height of the triangles denotes ± SE

a negligible amount of the gamma radiation from ^{131}I ($\mu_c \approx 0\,1$ cm /g) and transmits less than 2 % of the beta radiation from ^{131}I an amount which is negligible in the present connection background blackening is thus obtained under the strip of copper The whole batch was then dipped into a Na ^{131}I olution with a known concentration of activity determined by the 4 π technique The dimensions of the beaker were large enough for the olution to be regarded as an infinite beta ource The polythene disc acted as an infinite β reflector and reduced the solid angle for the incident beta radiation to 2π It was thus possible to calculate the β dose in the film emulsion (WALINDER 1957) Direct contact between film and radioiodine olution was excluded by covering the entire film with tape to prevent a rapid exchange of the radioiodine of the olution and the bromide of the film

The blackening values obtained by subtracting the blackening under the copper trip from the corresponding values in the film surfaces that had been covered by the tape steps only were plotted in a lin log diagram with the thickne s of the ab orber as the abscissa The film blackening corresponding to the surface dose of the semi infinite radiation source was determined by extrapolation to the ab orber depth 0 and correction for deviation from the exponential shape at mall ab orber depths according to LOEVINGER et coll 1956) The calibration film was always developed and fixed with the experimental film







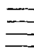






Fig 1 Arrangement for exposure of the calibration film The film and the tape layers were 0 17 mm thick The thickness of the Cu strip was 0 10 mm For the sake of clarity the thickness of film tape layers and Cu strip have been enlarged The back ground blackening of the film is obtained under the copper strip

film blackening and surface dose, as well as the tissue equivalence in film base and Mix D have been discussed in an earlier paper (WALINDER 1957)

The remaining frozen tissue was allowed to thaw and measured for activity following the exposure The activity values were compared with the above mentioned measurement of the whole lobe (or neck) and with the values obtained by measuring an aliquot part of the injection solution The film was checked as regards ^{131}I contamination by making activity measurements immediately before it was developed The connection between β doses from ^{131}I and the corresponding film blackenings was obtained by exposing calibration *films to semi infinite ^{131}I solutions and correcting the results* thus received for the contribution from γ rays

The calibration film was exposed in the following way A strip of film, about 1 cm wide, was covered with a few layers of water resistant, light proof tape arranged on top of one another in the form of steps A strip of copper, 2 mm wide and 0 1 mm thick, was placed between the film and the layers of tape The film, copper strip and tape were mounted on a 2 mm thick polythene disc with the film nearest the plate (Fig 1) *The strip of copper absorbs only*

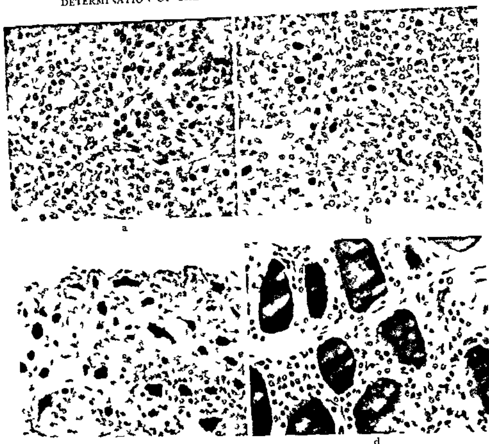


Fig 3 Development of thyroid tissue in foetuses and young mice PAS × 312 a) Foetus 17 days after conception No colloid Several mitotic figures present b) Foetus 18 days after conception Scattered small colloid islets c) Newborn 1 day old mouse Colloid islets still el ti el sparsel scatte ed in a tissue matrix consisting of epithelial cells in a state of active proliferation d) A 60 day old mouse The tissue is mature Follicles well separated from one another by layers of stroma cuboidal epithelium Mitoses are rare

effect on the dose calculations In foetuses and young mice however the increase in thyroid volume during the ^{131}I exposure substantially influences the dose Moreover in heavily irradiated foetal thyroids the inhibited neonatal growth of the glands has a considerable effect upon the total integrated dose

Uptake and retention of ^{131}I Adults It was in most cases desirable to irradiate the thyroid gland as selectively as possible without exposing other organs to irradiation As the uptake of iodine by the thyroid largely depends on the

Results and Discussion

Growth and ^{131}I accumulating capacity of mouse thyroid

The following parameters were examined (1) the development of the thyroid gland as a function of age, (2) the uptake and retention of ^{131}I as a function of (a) the iodine content of the diet, (b) diurnal and seasonal variation, and (c) the thyroid development in foetuses and young mice

The weight of the thyroid gland The thyroid weight increased in the CBA mouse during the whole of the first year of life During the last three days in utero and the first two weeks of life, this weight increase is fairly exponential (Fig 2) No sexual differences were evident in the thyroid development during the first month of life After this first exponential period the growth rate decreased (more rapidly in females than in males) The weight of the thyroid decreased slightly in the old mouse after it had reached the age of about 1 5 years (Fig 2) This decrease was probably the result of seasonal influences rather than an ageing effect (WALINDER et coll 1971) The very rapid development of the foetal thyroid tissue is evident from Fig 3

Only in about one case in every ten was there any sign of colloid in the 17 day old foetus whereas colloid islets were present without exception in the 18 day foetus The foetal age was determined by establishing the time when a vaginal plug appeared A control for the presence of a vaginal plug was carried out every morning Thus, as this control was done only once a day, the fact that colloid was present in all cases on the 18th gestation day but only in a few cases on the 17th day must imply that extremely rapid colloid synthesis took place Coitus may have occurred at any time from the morning of the day before the vaginal plug was observed, in other words 0 to 24 hours before the day, called here the 1st day of gestation

The lively activity in the gland manifests itself in extremely high mitotic frequency The dividing cells to be seen in sections from 18 day old foetuses (or later) lie mostly between the follicles The mouse thyroid is still irregular at birth and the colloid bearing follicles are sparsely distributed in a tissue matrix consisting mainly of epithelial cells in a state of active proliferation

The colloid in the 60 day old mouse occupies about 40 % of the glandular volume and the follicular epithelium is cuboidal With increasing age, the proportion of colloid increases, so that in a 1 year old animal the follicles have expanded and the follicular epithelium has flattened into a narrow ring of cells around the colloid which now occupies 70 to 80 % of the total thyroid volume (WALINDER et coll 1971) No further colloid synthesis would appear to take place after about 1 5 years of age, however

The changes in thyroid size in adult mice usually have only a negligible

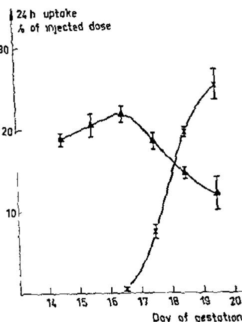


Fig 4 The 24 hour uptake in mothers and litters in relation to the day of gestation The triangles denote the mothers uptake and the crosses the total uptake of the litters The vertical lines through the mean values denote ± SE

One and the same dose of iodine (0 25 μCi ^{131}I per mouse) was given to mice at 8 a m 1 p m and 4 to 5 p m to test any diurnal effects on the uptake of ^{131}I The experiments were carried out at three different seasons The uptake values obtained appear in Table 2 the animals were 70 to 90 days old The table indicates that the 24 hour uptake of ^{131}I injected at 1 p m was significantly greater than the corresponding uptake of radioiodine injected at 4 p m This difference was not influenced by increasing the iodine concentration in the food from 0 33 to 0 74 μg per g of pellet (as shown by the figures from December 1966) nor was it influenced by any seasonal variations

Foetuses The uptake in foetuses was investigated after the intravenous injection of the mothers The mothers were fed from the first day of pregnancy on pellets poor in iodine (Ewos II)

The thyroid glands of mice at an age of 2 months born to mothers maintained on an iodine poor diet from the first to the 18th day of pregnancy have on an average the same thyroid weights and histologic appearance as those normally present in mice of this age Nor is it possible to record any appreciable alteration in the thyroid s ability to accumulate ^{131}I or in the reaction to propylthiouracil treatment However in adult mice maintained from the

Table 2

The diurnal variations of the 24 hour uptake of ¹³¹I by the thyroid gland There is a highly significant difference between the 24 hour uptakes of ¹³¹I when injected at 1 p m and at 4 (5) p m This difference is not influenced by increasing the iodine concentration in the food from 0 33 to 0 74 µg/g (as indicated by the figures from December 1966) nor is it influenced by any seasonal variation

Date	Time of injection	No of animals	Iodine conc in the food µg/g	24 hour uptake % of injected activity (±SE)
Dec	8 a m	10	0 33	35 8 ± 2 2
21	1 p m	10	0 33	42 0 ± 1 4
1966	4 p m	10	0 33	31 5 ± 1 7
Dec	8 a m	10	0 74	18 3 ± 1 0
30	1 p m	10	0 74	19 3 ± 1 6
1966	4 p m	10	0 74	12 3 ± 0 8
Sept	8 a m	5	0 70	22 4 ± 1 5
30	1 p m	14	0 70	25 5 ± 1 2
1967	4 p m	14	0 70	18 3 ± 1 0
June	8 a m	10	0 50	28 7 ± 1 3
17	1 p m	10	0 50	29 7 ± 0 9
1968	5 p m	10	0 50	21 6 ± 0 6

iodine content of the diet, the requirement of selective thyroid irradiation could be met by feeding the animals temporarily on a diet with a low iodine content (The iodine content of the S diet — about 27 µg I per g of pellet — is high in comparison with what is usually considered the optimum for other animal species and it ensures a daily supply of approximately 40 µg of iodine per animal SPECTOR (1956) states, however, that for maintenance and normally vigorous activity of male adult mice a daily supply of 1 300 µg of iodine per kg body weight is required, this corresponds to 30 to 45 µg of iodine per day to the CBA mouse)

A compilation of the uptake values obtained 24 hours after intraperitoneal injections of ¹³¹I (injections performed between 8 a m and 9 a m) to mice 70 to 90 days of age furnished the relations between the iodine content of the diet and the 24 hour uptake (Table 1) The animals had all been maintained on the S diet (Standard pellets) from birth This diet was changed for Ewos and S I pellets 14 days before the uptake measurements It was also found that the uptake depended to a large extent on the time of day when the injection was performed, an observation that possibly may have some connection with the marked 24 hour rhythm of the CBA mouse

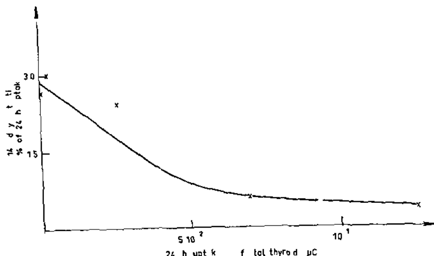


Fig 6 The 14 day retention of ^{131}I expressed as a percentage of the amount of radioiodine in the thyroid gland of the 19 day old mouse foetus Different amounts of ^{131}I were administered to the foetuses by intravenous injection of the mothers on the 18th day of gestation Every point in the diagram is based on mean values from four litters (or more)

whole body measurements some time after birth so that individuals with extremely low uptakes can be excluded when dose effect relations are to be investigated

The ability of the foetal thyroid to accumulate iodine is intimately connected with the inception of colloid formation (Figs 3 4)

Fig 5 indicates the uptake and retention for adult mice and for mother and litter after the intravenous injection of mothers on the 18th day of pregnancy The decrease in thyroid activity was at first more rapid in adult mice kept for 14 days or longer on an iodine poor diet than in those maintained continuously on a normal diet The diet was in these animals changed to the normal one 24 hours after the radioiodine injection After approximately one week the retention curve for the mice fed on an iodine deficient diet prior to the injections of ^{131}I ran parallel to that obtained for the animals on the iodine rich diet The uptake for mothers injected with ^{131}I on the 18th day of pregnancy was lower than for non pregnant females but the retention curve otherwise had the same shape as for the mice given the iodine poor diet During the remaining two days of pregnancy the retention curve was the same for litters as for the mothers From birth onwards however the ^{131}I concentration in the thyroids of the litters decreased rapidly The retention of iodine in the

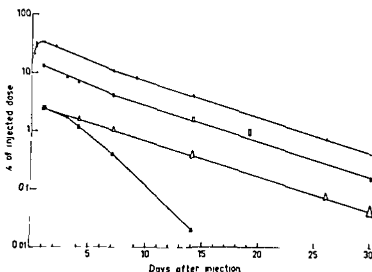


Fig 5 The ^{131}I activity in the thyroid glands expressed as percentage of injected activity Dots denote experimental values and *their vertical extensions* ± *SE solid rectangles indicate values* for adult CBA males The mice were on an iodine poor diet for 14 days before the injection and one day after injection it was changed to iodine rich pellets White rectangles denote experimental values in mothers injected with ^{131}I on the 18th day of pregnancy and maintained from the first day of pregnancy on Ewos II One day after the injection this was changed to the standard pellets White triangles denote values for adult mice maintained from birth on the S diet and solid triangles experimental values for foetuses (newborns) these animals received high doses of ^{131}I by intravenous injection of the mothers on the 18th day of gestation The lines correspond to the parameters given in Table 3

time of weaning and onwards on an iodine poor diet both body weights and thyroid weights are lower than in mice given a normal diet In such animals the growth of the thyroid gland cannot be induced by goitrogenic treatment although it may be achieved by supplying iodine with the diet (WALINDER, unpublished)

The ability to accumulate iodine begins relatively late in the CBA foetus Not until the 16th to 17th day of gestation was it possible to establish with certainty an uptake of ^{131}I in the thyroids of the foetuses after intravenous injection of the mother (cf Fig 4)

The thyroidal cumulative ability increased rapidly from the 17th day after conception and onwards while at the same time the mother's uptake decreased The total uptake of the litter reached the same value as the mother's between the 18th and 19th day of gestation and continued to rise until birth The uptake of ^{131}I in different foetuses in one and the same litter varied in approximately the same way as in different adult individuals Monozygotic twins however, usually each take up much smaller amounts of radioiodine than other siblings in the same litter Such variations can be checked by means of

do e) is equal to the energy emitted per gram The dose in infinite radiation ources is usually calculated on this basis For the concentration of activity 1 μCi/g the following is obtained when $\bar{E}_\beta$ for ^{131}I $= 0\ 188$ MeV and 1 MeV/g $= 1\ 6\ \ 10^{-8}$ rad

$$D_\beta = 3\ 7\ \ 10^4\ \ 0\ 188\ \ 1\ 6\ \ 10^{-8}\ \ 3\ 600 = 0\ 40 \text{ rad}/\mu\text{Ci h)}$$

In accordance with the above formula the blackening values of the calibration films obtained could be well fitted with straight lines when plotted in lin log diagrams as functions of the thickness of the tape layers As the tape was 22 mg/cm thick the blackening value under the first layer should not lie exactly on the straight line drawn through the points from greater ab orber depths the deviation is o small however that it could not be verified experimentally Extrapolation of the line obtained to the ab orber depth 0 produces an important error however, as the curve close to the ource of radioactivity bends steeply upwards LOEVINGER et coll (1956) gave the following correction factor between extrapolation value and dose at the surface of a emi infinite beta ource

$$\frac{I}{ae} = 1\ 41 \text{ (for } ^{131}\text{I)}$$

Thus the extrapolation value for the exponential curve at the ab orber depth 0 must be multiplied by 1 4 in order to obtain a blackening corresponding to the do e in the semi infinite ^{131}I ource (D_β) For Cine Positive No 5302 film this relation between D_β and the corresponding film blackening varied slightly with the age of the developing fluid temperature and o on but as a rule darkening 1 was obtained for a dose of 67 rad at the readings in the microphotometer used in the laboratory

Determination of the dose distribution in the thyroid Fig 7 indicates the dose di tribution along a line through the thickest part of a lobe and perpendicular to its longitudinal axis 24 hours after the injection of ^{131}I into a 70 day old mouse The curve has been obtained from microphotometric measurements of a film exposed to a lobe embedded in ice and sectioned to its plane of symmetry The dose is seen to be fairly homogeneous all over the half lobe examined but is decreasing towards the edges of the lobe where it is about 40 % of that in the centre

The thyroid of the mouse is too mall to be considered an infinite beta ource The maximum dose in the thyroid model u ed by LOEVINGER et coll (1956) was 75 % of the beta dose in an infinite source with the same concentration of radioactivity as that in the thyroid In the case illustrated the thickness of the

thyroid glands of newborn mice is highly dose dependent The decrease of ^{131}I in heavily irradiated glands of such mice is more rapid than in those irradiated with low doses Fig 6 *presents the 14 day retention as a function* of the thyroid content of ^{131}I in 19 day old foetuses, i e as a function of the *24 hour uptake*

The amount of ^{131}I transmitted via the mother's milk is not negligible In order to investigate how much of the activity given to the mother was passed to the litter through the milk, 0 1 μCi ^{131}I was injected on the 18th day of pregnancy into 11 females The new born mice were exchanged immediately after birth, so that a mother injected with ^{131}I suckled a litter that had been born at the same time as her own litter but whose mother had not received radioiodine The last named mother suckled the ^{131}I bearing litter After three days suckling the originally activity free litter had a thyroidal uptake that was about 20 ± 1 % of the activity measured in the suckling mother's own litter

Normally, the thyroidal activity in the mice that had received ^{131}I through the mothers on the 18th day of gestation decreased more slowly during the first week of life than in later weeks if they were suckled by their own mothers (Fig 5) This change in the retention curve is obviously caused by ^{131}I being passed to the offspring via the mother s milk during the first days of suckling the retention curve of the ^{131}I bearing litter suckled by non injected mothers attained its final slope as early as the first day of life

Film dosimetry

The gamma dose to an organ so small as the mouse thyroid from ^{131}I accumulated in the gland is entirely negligible as compared with the beta dose (WALINDER 1955 1957) The following film measurements therefore exclusively comprised determinations of beta doses

Evaluation of the calibration film At the distance x g/cm² from a semi infinite ^{131}I water solution, the dose in water according to LOEVINGER et coll (1956) is

$$D_\beta(x, \infty) = 0\ 5\ D_\beta\ a\ e^{1-\nu x}, \text{ if } \nu x \geq 2 \text{ (i e } x \geq 50 \text{ mg/cm}^2\text{)}$$

where $a = \frac{1}{3\ 84}$ for ^{131}I $\nu = 40$ cm²/g, and D_β is the dose inside an infinite, homogeneous radiation source For a ^{131}I water solution, $D_\beta = 0\ 40\ \sigma$ rad/h where σ is the activity per g of water expressed in μCi (Inside a radiation source with homogeneously distributed activity the radiation field is uniform at a distance from the surface of the source which is greater than the maximum range of the radiation i e Div $E = 0$ where E is the radiation energy This means that the radiation energy absorbed per gram of source material (i e the

The fairly smooth curve in Fig 7 means however that the contribution of radiation from underlying tissue compensates in large measure for local variations in the distribution of activity Moreover the release of radioiodine from the small follicles is more rapid than that from the large ones (WALINDER et coll) which means that the integrated dose will be more homogeneous than the dose distribution at a certain point of time after the administration of ^{131}I would suggest

The aperture of the diaphragm in the microphotometer measured 30 $\mu \times$ 30 μ In other words this opening had the same dimensions as the smaller follicles in the thyroid of the adult CBA mouse As the thyroid follicles in foetuses and young mice are usually smaller however the dose to the foetal and juvenile thyroid could only be measured in interfollicular areas

The thyroid gland in foetuses and young mice is too thin to allow irregularities in the activity distribution to receive full compensation with respect to the dose from surrounding tissue This is of course connected not only with the inconsiderable thickness of the remaining parts of the lobe but also with the fact that in the foetus and young animal the colloid islets lie sparsely scattered and not closely packed like the follicles in the adult animal The dose estimation is therefore subject to much greater uncertainty in the young animal than in the adult

Measurements of the film blackening after exposure to thyroid lobes from 3 newborn mice indicated that calculations based on the assumption that the dose is homogeneously distributed in the tissue overestimates the dose to central interfollicular areas by 17 to 25 % It was not possible to determine the details of the dose distribution

Dose calculations

For dose calculations it is necessary to be able to approximate experimentally obtained retention curves to mathematical functions Fig 5 indicates that this could be done with a fairly high degree of accuracy by using a series of exponential functions The corresponding retention parameters are given in Table 3

Adults The relatively homogeneous dose distribution in central parts of the thyroid lobe in adults made it possible to determine a maximum dose in the gland on the basis of LOEVINGER's model but with consideration paid to the slightly larger size of the thyroid in the CBA mouse

Assuming that the dose at the centre of the lobe is 80 % of the dose in an infinite ^{131}I source (D_β = 9 6 rad/day for 1 μCi ^{131}I per g of tissue) with the

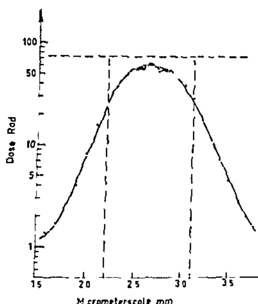


Fig 7 Microphotometric measurement of a film exposed to a lobe embedded in ice and sectioned to its plane of symmetry The peaks at the top of the curve apply to areas of the film that lay over follicular colloid in the central parts of the gland The blackening was read off by moving the aperture of the diaphragm 0 1 mm between each reading The distances between the readings were made shorter at the centre the aperture being moved 10—20 μ (Aperture 30×30 μ) The vertical broken lines denote the edges of the gland and the horizontal broken line the calculated value for D_β

half lobe was approximately 0 5 mm or — assuming the density of the thyroid tissue to be 1 g/cm^3—50 mg/cm

The centre dose in the gland whose dose values are given in Fig 7 was approximately 60 rad The weight of the lobe was 1 5 mg, the exposure time was 24 hours, and the activity in the lobe was measured as being 16 μCi g For a *semi infinite radiation source with this concentration of activity* the surface dose, with an exposure of 1 day, will be $0\ 5\ \ D_\beta\ \ 16\ \ 24\ \dfrac{1-e^{-\lambda}}{\lambda} = 74$ rad where λ is the decay constant for ^{131}I and D_β is the beta dose rate (rad/h) in an infinite water source containing 1 μCi ^{131}I per g The ratio between measured dose and semi infinite dose is thus 81 % Repeat tests with 11 glands (22 lobes) *from mice 70 to 90 days of age carried out under the same experimental* conditions as the example presented give a mean dose in the central gland of 80± 3 % (± SE) of what the dose in a semi infinite radiation source would have produced with corresponding activity concentrations

This mean value is higher than the figure given by LOEVINGER et coll (75 %) However, the thyroid lobe model suggested by LOEVINGER et coll is smaller (0 92 mg) and more elongated than the more ellipsoidal, 1 5 mg lobe of the 70 day old CBA mouse The solid curve in Fig 7 is fairly consistent with that calculated by LOEVINGER et coll for spheres

Radioiodine that has been taken up by the thyroid gland is inhomogeneously distributed *in the tissue One day after an injection the concentration* of radioiodine is higher in the small than in the large follicles (WALINDER et coll 1971)

extremely rapid in those animals that had received a diet poor in iodine for 14 days or longer (cf Fig 5) The retention curves presented a smoothing tendency for the large t s In view of the relatively rapid physical decay of ^{131}I this smoothing tendency was of little significance

Foetuses and juveniles As mentioned above dose measurements are more difficult to perform in foetu es Autoradiographs of thyroid sections from 1 week old mice given ^{131}I by intravenous injection of the mothers on the 18th day of gestation had blackening all over the cut surface Although this blackening was still slightly inhomogeneous newly synthesized colloid had obviously received a part of the radioiodine assimilated in the growing gland probably via the reutilization of ^{131}I from thyroid hormone already secreted

Film measurements indicated that a calculation model of the same type as that used for adult animals overestimates the dose by about 20 % in interfollicular areas i e in areas where the most actively proliferating cells are to be found

When the do e from ^{131}I to the small thyroid glands in mou e foetuses and juveniles is to be calculated the correction constant that must be used in order to compen ate for the deviation from an infinite beta ource may be based on the following rea oning A thyroid lobe in an 18 day foetus weighs about 0 1 mg and increa es fairly exponentially to approximately 0 18 mg by the 6th day of life The radius in a sphere (with the density 1 g/cm^3) that enlarges from 0 1 mg to 0 18 mg increase from 0 29 mm to 0 35 mm According to LOEVINGER et coll (1956) the do e at the centre of such a sphere is 0 56 D_β In the present calculations consideration was paid to the aforementioned 20 per cent correction for the dose in interfollicular tissue and D_β (9 6 rad/day μCi) was thus multiplied by 0 45 (instead of 0 80 for the adult mouse) The aforementioned do e formula could thus be used in calculating the dose to the interfollicular central parts of the foetal thyroids The dose to the peripheral parts of the e glands is 50 % of that in the centre (LOEVINGER et coll 1956) In the thyroid tissue closely surrounding ^{131}I bearing colloid islets the dose is much higher than that calculated for interfollicular areas The dose in such hot spots could not be determined with the methods presented Except for periods of constant thyroid weights due to heavy irradiation of the glands the thyroid growth may be written (cf Fig 2)

$$m(t) = 0\,2 \quad \exp(0\,083t)$$

where the figure 0 2 is the thyroid weight (at $t = 0$) of an 18 day old foetus The growth of heavily irradiated foetal thyroid glands is stopped very quickly and the weight of the glands remains fairly constant for ome days Thyroid growth tarts again after this period of arrest — the length of which

Table 3

Retention parameters, obtained from fig. 5 by regression analysis. k_i is the sum of the physical decay constant of ^{131}I and the thyroidal release rate constant during the period $t_{i+1}-t_i$. U_i is the fraction of the originally injected amount of ^{131}I remaining in the thyroid on day t_i

Periods of time	Day 1—3		Day 3—7		Day 7	
	U_1	k_1	U_3	k_3	U_7	k_7
Adult mice	0.33	0.19	0.23	0.19	0.11	0.14
Mothers	0.13	0.19	0.09	0.19	0.042	0.14
Offspring (foetus)	0.025	0.19	0.017	0.36	0.0041	0.43

same activity concentration (expressed in μCi/g) the following equation will be obtained

$$D_{max} = 9.6 \cdot 0.80 \sum \left[U(t_i) \int_0^{t_{i+1}-t_i} \frac{e^{-k_i t}}{m(t)} dt \right] \text{rad}$$

where k_i represents the retention constants (i.e. the sum of the physical decay constant and the thyroidal release rate constant for ^{131}I), $U(t_i)$ the ^{131}I activity in the gland on day t_i, and $m(t)$ is the thyroid weight at time t. The parameters in this formula vary from experiment to experiment. A set of parameters, obtained from Fig. 5 appear in Table 3. When these parameters are introduced into the above formula the following is obtained for adults

$$D_{max} = 18 \frac{Q}{m} \text{rad}$$

where Q is the amount of ^{131}I injected expressed in μCi and m the fairly constant thyroid weight in adults ($Q \approx U_1 = U(0)$). Fourteen days after the injection, 88 % of this infinity dose has been given off to the thyroid gland, and after a month the figure is 99 %.

It should be stressed that the procedure of replacing the retention curves with exponential curves is an approximation. No consideration was paid, for instance, to the fact that the radioactivity in the thyroid reaches its maximum value only 24 hours after the injection. However, assuming a constant activity in the thyroid gland during the first 24 hours following the injection (i.e. by taking $U(0) = U(1)$ and $k_0 = 0$) does not cause any appreciable error in the integrated total dose (< 2 %). The uptake during the first 24 hours was

measurements carried out by pressing a stack of films directly against a frozen ^{131}I solution with a well known concentration of activity indicated that $2 > c > 1.8$ which implies that the underestimation of the dose (if any) cannot be greater than 6 %. The accuracy of the other constants in the formula (ν and a) is much higher than that of c. It should be emphasized that the calculated doses given are maximum doses to the centre of the thyroid. The dose decreases towards the periphery of the gland where it amounts to only 40 % of the maximum dose in adult mice (cf. Fig. 6) and to 50 % of the maximum interfollicular dose in foetal and juvenile mice (LOEVINGER et coll. 1956). It should also be borne in mind that the dose to the foetal and juvenile thyroid tissue closely surrounding ^{131}I bearing colloid islets is higher than the calculated maximum dose to the interfollicular areas.

Acknowledgements

The author is indebted to Mr R. Hesbol, AB Atomenergi, for the activation analyses and to Miss A. M. Sjoden and Mr C. J. Jonsson for their technical assistance.

SUMMARY

The radiation dose to the thyroid glands in foetal and adult mice after injections of ^{131}I has been calculated by a mathematical model based on film measurements in excised glands and determinations of the thyroidal uptake and retention of the nuclide. The present measurements confirmed LOEVINGER's semitheoretic determinations of the β dose to the adult mouse thyroid.

ZUSAMMENFASSUNG

Die Strahlendosis der Thyreoidea der fetalen und erwachsenen Maus nach Injektion von ^{131}I wurde durch ein mathematisches Modell berechnet, das sich auf Filmmessungen der exzidierten Thyreoidea und Bestimmungen der Aufnahme und Auflagerung des Nukleids in der Thyreoidea stutzt. Die vorliegenden Messungen bestatigen die semitheoretischen Bestimmungen von LOEVINGER der β-Dosis der Thyreoidea der erwachsenen Maus.

RÉSUMÉ

La dose d'irradiation de la glande thyroïde de foetus de souris et de souris adultes apres injection de ^{131}I a ete calculee grace à un modele mathematique base sur des mesures sur film de glandes extirpees et sur des mesures de la fixation et de la retention du nuclide par la thyroide. Ces mesures ont confirmé les determinations semi-theoriques de LOEVINGER de la dose β à la thyroide de la souris adulte.

depends on the dose — and soon shows approximately the same rate as in unirradiated animals (WALINDER, unpublished)

The above dose formula for adults may thus be applied to determination of the dose to the interfollicular areas in foetal and juvenile thyroids by exchanging the correction constant 0 80 for 0 45 and by adding the growth constant 0 083 to the retention constants λ_i

The ^{131}I dose to the foetal thyroid gland decreased very rapidly According to the figures above and those given in Table 3, more than 50 % of the 'infinity dose has been given off to the foetal thyroids two days after the injection of the mothers (i e at the birth of the mice) and after 3 days the corresponding figure is 96 %

Discussion of errors The standard error inherent in the estimation of the mean value of the ratio between central thyroid doses and doses within 'infinite ^{131}I sources (0 80) amounts to ± 4 % for adult animals A corresponding control of the relation between measured and calculated dose in the young mouse is more difficult, mainly because the thyroid tissues cannot be weighed but have to be estimated from serially sectioned glands, as described earlier However, measurements of the film blackening over interfollicular areas in the foetal thyroid indicate that the corresponding ratio value for these areas (0 45) would imply an error of less than 10 %

The most important errors inherent in the calculation procedure described lie in the variations in the biologic parameters uptake and thyroid weights The standard deviation in both cases is about 20 % However as a certain degree of positive correlation exists between uptake and thyroid weight it has been found that the standard deviation for the activity concentration, $U(t_i)/m$ is if anything slightly less than 20 % The retention approximations and the error inherent in the film calibrations are wholly negligible as compared with the biologic deviations It would thus seem logical to count on a standard deviation from the calculated dose values of ± 20 % for both adult and young mice as well as for foetuses, provided that animals that have proved at whole body measurements to have extremely low uptakes (monozygotic twins) are eliminated The formulas mentioned should thus be capable of providing a relatively good basis for comparisons in the assessment of the effects of irradiation, if the doses calculated from them are based on average values from experiments with fairly large series of animals Uptake and retention should be followed up in parallel experiments in control groups

In addition there might be a systematic error involved in the correction of the extrapolated blackening of the calibration films The value of the constant c (= 2) in the correction formula as proposed by LOEVINGER et coll (1956) for ^{131}I may be a little high and lead to an underestimation of the dose Film

FROM THE DIVISION OF RADIOBIOLOGY THE RESEARCH INSTITUTE OF NATIONAL DEFENCE SUNDBYBERG SWEDEN

EFFECT OF IRRADIATION ON THYROID GROWTH IN MOUSE FOETUSES AND GOITROGEN CHALLENGED ADULT MICE

by

G WALINDER and ANNE MARIE SJODEN

Proliferating tissue displays greater sensitivity to ionizing radiation than cell populations in a more steady state of growth a rule that probably applies with few exceptions It is therefore important that special consideration should be paid to the unborn and the young when the probable consequences to a civilian population of reactor accidents and nuclear explosions are being assessed this also applies when suitable measures for counteracting such hazards are under discussion The international norms usually applied in the evaluation of radiation risks suggest that the radioiodines often determine the maximum permissible concentrations of airborne fission products and hence the demands for tightness and tenacity of reactor containments as well as the extent and duration of restrictions on food consumption evacuations and the like

It seems generally agreed today that roentgen irradiation of the thyroid gland in infancy increases the risk of thyroid carcinoma in later life (WARREN 1966 HEMPELMAN et coll 1967 DOLPHIN 1968) CONARD et coll (1966) noted a very high incidence of nodules among young people who were living on the Rongelap

Submitted for publication 15 October 1970

REFERENCES

JONES D E A and RAINE H C Letter to the Editor Brit J Radiol 22 (1949), 549

LOEVINGER R, JAPHA E M and BROWNELL G L *Discrete radioisotope sources Chap 16 In* Radiation dosimetry Edited by G J Hine and G L Brownell Academic Press New York 1956

NOTTER G und WALINDER G Dosismessungen an ^{90}Y Kugeln zur Ausschaltung der Hypophyse Strahlentherapie 110 (1959) 95

ROMEIS B Mikroskopische Technik Leibniz Verlag Munchen 1948

SPECTOR W S Handbook of biological data Table 166 p 196 Saunders & Co Philadelphia and London 1956

TONNA E A Osteoclasts and the ageing skeleton A cytological cytochemical and autoradiographic study Anat Rec 137 (1960), 251

WALINDER C Colloidal $^{6}As\ S_3$ Its production and possible use in the treatment of papillomatosis of the urinary bladder Acta radiol 44 (1955) 521

— Measurements of relative beta depth doses in tissue equivalent material Acta radiol 48 (1957) 68

WALINDER G SJODEN A M and JONSSON C J Ageing processes in the thyroid gland of the CBA mouse FOA Reports Vol 5 1971

dissolved in 0 9 % saline Propylthiouracil (AB Pharmacia Uppsala Sweden) 0 1 % was administered to the animals in drinking water The latter was made slightly alkaline (pH 8 to 8 5) in order to prevent precipitation of the PTU The iodine content of the diet was determined by activation analysis at AB Atomenergi Studsvik, Sweden

Dose calculations

The determination of the dose to the thyroid gland was carried out in accordance with the formulas in an earlier paper (WALINDER 1971) The iodine concentration in the pellets was not constant during the course of the experiments and consequently the uptake and retention of ^{131}I in the thyroids varied somewhat from time to time Consideration had also to be paid to the interdependence between the ^{131}I dose and the thyroid growth rate as well as to the fact that the hormonal secretion rate increased with the dose The parameters necessary for dose calculations — uptake retention size of the thyroids, etc — were accordingly not identical with those given in the earlier paper (WALINDER 1971) This underlines the importance of making dose calculations and not merely relying on the dose being proportional to the amount of radioactivity injected

For determination of the activity in the thyroid the glands were removed hydrolyzed in 1 ml conc NaOH and measured for activity in a well type crystal connected to a two-channel scaler (Picker Twinscaler II) The difficulties in carrying out in vivo measurements of ^{131}I in the thyroid glands of mice necessitated the uptake and retention being determined by in vitro assays in thyroid glands excised from mice in a special retention group kept parallelly with the experimental groups The animals were killed with chloroform

The doses in Tables 1 to 4 are means to the centres of the glands ($\bar{D}_{m}$) The dose in the thyroid decreases towards the periphery of the gland so that at the edge of the thyroid it is approximately 0 4 D_{max} in adults and 0 5 D_{m} in foetuses and juveniles

Experimental procedures

The experiments with ^{131}I were divided into four groups

Foetuses The foetuses were given ^{131}I by intravenous injections to the mothers on the 18th day of gestation The mothers were maintained on an iodine deficient diet (0 3 μg iodine per g pellet) from the first day of pregnancy from the 19th day of pregnancy and onwards the food was iodine enriched (standard diet ca 27 μg I per g pellet)

atoll at the time of the nuclear weapon test at Bikini in 1954 and who were then under 10 years of age The high incidence of thyroid changes among the children 11 years after exposure, the only persisting evidence of injury, indicates that even after a short term exposure to radioiodine in combination with non lethal external doses, the growing thyroid may be a 'critical organ' in young people exposed to radioactive fallout It is not possible, however, to make direct comparisons between the dose of ^{131}I, effect, and age, from these observations as the external gamma radiation had probably played a considerable part in producing the end result

A large number of animal investigations have disclosed that the growing thyroid gland is especially sensitive to radiation from ^{131}I accumulated in the gland, and not least in the carcinogenic effect of the irradiation Growth was usually provoked in adult animals by increasing the TSH content of the blood, this was effected either by subtotal thyroidectomy (GOLDBERG et coll 1964), by means of goitrogenic stimulation (DONIACH & LOGOTHEOPOULOS 1955, DONIACH 1963, LINDSAY & CHAIKOFF 1964), or by feeding with an iodine deficient diet (AXELRAD & LEBLOND 1955) A connection between thyroid growth, radiation, and incidence of thyroid neoplasms probably also exists in adult man (DONIACH et coll 1966)

The present investigation was concentrated on the effect of ^{131}I on the normal and propylthiouracil (PTU) stimulated growth of the thyroid in foetuses and young mice These dose effect relations were compared with the corresponding connections between dose and impairment of the goitrogenic response in adult mice The radiation effect on the PTU stimulated glands in adult mice was investigated as a function of the time interval between ^{131}I injection and the commencement of the PTU treatment as well as a function of the iodine content of the food In addition, the effect of ^{131}I was compared with that of irradiation with roentgen rays in adult mice

^{131}I experiments

Animals and Materials

Both sexes of CBA mice were examined in the experiments with foetuses while only males were used in the investigation in adults One mother (with her litter) was accommodated in each cage during the gestation and suckling periods After weaning and in the adult series, 10 (or less) animals were housed in each cage The animals were kept in thermostat regulated rooms with controlled humidity in which the lights were automatically turned on at 6 a m and off at 6 p m

The ^{131}I solutions injected consisted of carrier free Na^{131}I (from the Radiochemical Centre, Amersham England and AB Atomenergi, Studsvik, Sweden)

Table 1

Body and thyroid u eights (±SE) in 2 month old mice gi en different amounts of ^{131}I by intravenous injec tion of the mothers on the 18th day of gestation P values obtained by Student s t test denote the significance of the grouth impairment in the irradiated thyroid glands in relation to the thyroid wei hts of the controls The three tables (A B C) present the results from three different experimental series runnin at different times

Inj I (μCi)	D̄ (rad)	Males				Females			
		No of animals	Body we ght (g)	Thyro d weight (mg)	p	No of an mals	Body weight (g)	Thyro d weight (mg)	p
A									
—	—	14	25 2±0 4	3 00±0 12		13	20 3±0 3	2 70±0 11	
1 0	1 900	17	25 0±0 4	3 05±0 12		19	?0 7±0 3	2 50±0 14	—
B									
—	—	46	23 1±0 2	2 80±0 7		5?	18 8±0 2	2 4?±0 05	
2 0	4 900	48	22 6±0 2	? 14±0 07	<0 001	48	18 1±0 2	1 99±0 98	<0 001
3 0	6 700	26	2? 9±0 4	1 71±0 10	<0 001	17	17 5±0 5	1 64±0 08	<0 001
5 0	11 000	23	2? 4±0 4	1 64±0 13	<0 001	36	17 8±0 ?	1 27±0 07	<0 001
C									
—	—	12	22 3±0 3	2 40±0 10		10	18 8±0 4	2 37±0 15	
? 5	3 700	20	23 2±0 4	1 97±0 08	<0 01	20	19 9±0 3	1 93±0 06	<0 01

Table 2

Rad ation effect on the increased thyroid grou th obtained by treatin young mice u ith PTU from the time of u eaning until they u ere killed at 50 days

Inj I (μCi)	$\bar{D}_m$ (rad)	Males			Females		
		No of animal	Thyro d weight (mg)	p	No of an mals	Thyroid we ght (mg)	p
A							
—	—	13	6 6±0 2		13	6 3±0 3	
0 5	1 000	10	7 0±0 5		10	6 0±0 3	
1 0	1 900	16	5 7±0 2	< 0 01	19	5 3±0 2	<0 01
B							
—	—	10	6 7±0 4		10	6 5±0 3	
2 0	4 900	17	4 8±0 2	<0 001	11	4 0±0 3	<0 001

mou e could not be observed with ^{131}I doses of the order of 2 000 rad (Table 1A Nevertheless ome action on the gland cells obviou ly occurs at doses of this magnitude as is evident from the fact that the PTU stimulated extra growth between the ages of 20 to 50 days was impaired (Table 2A)

Experiment 1 Different amounts of ^{131}I given to foetuses The experiment was carried out at three different times and the results are presented in three tables (1A, 1B, 1C) The animals in section 1A were killed at the age of 75 days and those in the two other sections at 60 days

Experiment 2 This experiment was identical with experiment 1 with the exception of further thyroid growth stimulation provoked by PTU in the drinking water for one month immediately after the weaning As this experiment was conducted at the same time as experiments 1A and 1B, the results are presented in a similar way in Tables 2A and 2B

Adult mice The adult mice were 75 to 87 days old at the start of the experiments They were fed on pellets with a low iodine content for 14 days, after which they were given ^{131}I by intraperitoneal injections Two experiments (3 and 4) were carried out to examine the significance of the time interval between irradiation and the start of the goitrogen challenge and the iodine content in the diet

Experiment 3 Different amounts of ^{131}I to adult mice As in experiment 1 this was divided into three series (3A, 3B, and 3C) The animals had been fed with an iodine deficient diet (0 3 μg I per g pellet) for 14 days before the ^{131}I injection following which the diet was changed to iodine enriched pellets (ca 27 μg I per g pellet) Fourteen days later, PTU was administered in the drinking water until later the animals were killed An additional control group of animals that received the iodine deficient diet was maintained during the entire course of the experiment

Experiment 4 Different amounts of ^{131}I to adult animals The animals were maintained on a diet fairly low in iodine (0 75 μg I per g pellet) during the entire course of the experiment PTU was given in the drinking water for 30 days from the day after the ^{131}I injection

Results

Experiment 1 Effects of ^{131}I on foetal and juvenile thyroid glands Significant effects on the thyroid growth in the foetus and young mouse could be observed with ^{131}I doses of 3 700 rad and higher to the centre of the thyroid glands (Table 1)

It should be stressed that the doses given in the tables refer to those delivered to interfollicular areas in the central part of the glands ($\bar{D}_{max}$) The dose to the epithelium surrounding the sparsely scattered follicles in the foetal thyroid is higher than the calculated value of $\bar{D}_{max}$ (WALINDER 1971)

Experiment 2 Effects of ^{131}I on PTU challenged foetal and juvenile thyroid glands A significant effect on the normal thyroid growth in the foetus and young

Table 1

Body and thyroid weights (±SE) in 2 month-old mice given different amounts of ^{131}I by intravenous injection of the mothers on the 18th day of gestation. P values obtained by Student's t test denote the significance of the growth impairment in the irradiated thyroid glands in relation to the thyroid weights of the controls. The three tables (A, B, C) present the results from three different experimental series running at different times

Inj. ^{131}I (μCi)	$\bar{D}$ (rad)	Males				Females			
		No. of animals	Body weight (g)	Thyroid weight (mg)	p	No. of animals	Body weight (g)	Thyroid weight (mg)	p
A									
—	—	14	25.2±0.4	3.00±0.12		13	20.3±0.3	2.70±0.11	
1.0	1 900	17	25.0±0.4	3.05±0.12		19	20.7±0.3	2.50±0.14	—
B									
—	—	46	23.1±0.2	2.80±0.7		52	18.8±0.2	2.42±0.05	
2.0	4 900	48	22.6±0.2	2.14±0.07	0.001	48	18.1±0.2	1.99±0.98	<0.001
3.0	6 700	26	22.9±0.4	1.71±0.10	<0.001	17	17.5±0.5	1.64±0.08	<0.001
5.0	11 000	23	22.4±0.4	1.64±0.13	<0.001	36	17.8±0.2	1.27±0.07	<0.001
C									
—	—	12	22.3±0.3	2.40±0.10		10	18.8±0.4	2.37±0.15	
2.5	3 700	20	23.2±0.4	1.97±0.08	0.01	20	19.9±0.3	1.93±0.06	<0.01

Table 2

Radiation effect on the increased thyroid growth obtained by treating young mice with PTU from the time of weaning until they were killed at 50 days

Inj. ^{131}I (μCi)	$\bar{D}_{\infty}$ (rad)	Males			Females		
		No. of animals	Thyroid weight (mg)	p	No. of animals	Thyroid weight (mg)	p
A							
—	—	13	6.6±0.2		13	6.3±0.3	
0.5	1 000	10	7.0±0.5		10	6.0±0.3	
1.0	1 900	16	5.7±0.2	<0.01	19	5.3±0.2	<0.01
B							
—	—	10	6.7±0.4		10	6.5±0.3	
2.0	4 900	17	4.8±0.2	<0.001	11	4.0±0.3	<0.001

mouse could not be observed with ^{131}I doses of the order of 2 000 rad (Table 1A). Nevertheless some action on the gland cells obviously occurs at doses of this magnitude as is evident from the fact that the PTU stimulated extra growth between the ages of 20 to 50 days was impaired (Table 2A).

Experiment 1 Different amounts of ^{131}I given to foetuses The experiment was carried out at three different times and the results are presented in three tables (1A, 1B, 1C) The animals in section 1A were killed at the age of 75 days and those in the two other sections at 60 days

Experiment 2 This experiment was identical with experiment 1 with the exception of further thyroid growth stimulation provoked by PTU in the drinking water for one month immediately after the weaning As this experiment was conducted at the same time as experiments 1A and 1B, the results are presented in a similar way in Tables 2A and 2B

Adult mice The adult mice were 75 to 87 days old at the start of the experiments They were fed on pellets with a low iodine content for 14 days, after which they were given ^{131}I by intraperitoneal injections Two experiments (3 and 4) were carried out to examine the significance of the time interval between irradiation and the start of the goitrogen challenge and the iodine content in the diet

Experiment 3 Different amounts of ^{131}I to adult mice As in experiment 1 this was divided into three series (3A, 3B, and 3C) The animals had been fed with an iodine deficient diet (0 3 μg I per g pellet) for 14 days before the ^{131}I injection following which the diet was changed to iodine enriched pellets (ca 27 μg I per g pellet) Fourteen days later, PTU was administered in the drinking water until later the animals were killed An additional control group of animals that received the iodine deficient diet was maintained during the entire course of the experiment

Experiment 4 Different amounts of ^{131}I to adult animals The animals were maintained on a diet fairly low in iodine (0 75 μg I per g pellet) during the entire course of the experiment PTU was given in the drinking water for 30 days from the day after the ^{131}I injection

Results

Experiment 1 Effects of ^{131}I on foetal and juvenile thyroid glands Significant effects on the thyroid growth in the foetus and young mouse could be observed with ^{131}I doses of 3 700 rad and higher to the centre of the thyroid glands (Table 1)

It should be stressed that the doses given in the tables refer to those delivered to interfollicular areas in the central part of the glands ($\bar{D}_{max}$) The dose to the epithelium surrounding the sparsely scattered follicles in the foetal thyroid is higher than the calculated value of $\bar{D}_{max}$ (WALINDER 1971)

Experiment 2 Effects of ^{131}I on PTU challenged foetal and juvenile thyroid glands A significant effect on the normal thyroid growth in the foetus and young

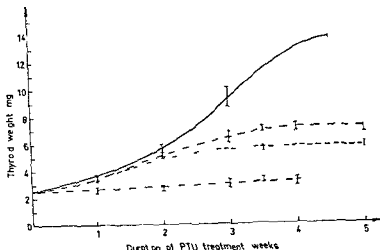


Fig 1 The increase in thyroid weight in mice (90 days of age at the start of the experiment) as a function of the duration of the PTU treatment The treatment procedures were 1 PTU + iodine deficient diet (———) 2 PTU alone ( ) 3 1 5 μCi ^{131}I ($\overline{D}_{max}$ = 4 000 rad) one day prior to the start of the PTU regimen ( ) and 4 unchallenged controls ( ) The vertical lines through the mean values denote ± SE

Experiment 3 Effects of ^{131}I on PTU stimulated adult thyroids Table 3 (A B C) indicates that the dose of ^{131}I necessary to produce significant impairment of goitrogen stimulated thyroid growth was of the order of 6 600 rad at the centre of the gland and around 2 600 rad at the periphery The range of error in the tables is the standard error of the mean the dose values are correct to two places Mice injected with 4 5 μCi ^{131}I which corresponded to an average dose at the centre of the thyroid of 14 000 rad had no histologically verifiable effects in the unchallenged thyroid 39 days after the injection (Table 3B)

Experiment 4 Effects of ^{131}I on PTU stimulated adult thyroids An additional experiment was carried out to investigate the significance of the time interval between the ^{131}I injection and the start of PTU treatment In this experiment the PTU treatment was started 24 hours after the ^{131}I injection but the mice were maintained during the entire course of the experiment on the same diet as that given before the PTU start this diet contained 0 75 μg iodine per g pellet The animals were injected with 1 5 μCi and 2 1 μCi producing a total dose to the central parts of the glands of 3 600 and 5 000 rad respectively The results are presented in Table 4

The increase in the thyroid weight is presented in Fig 1 as a function of the duration of PTU treatment in unchallenged animals as well as in animals given

Table 3

Body and thyroid weights (±SE) in adult male mice with PTU started 14 days after injection of varying amounts of ^{131}I As in the preceding tables, p denotes the significance of the growth impairment in the PTU challenged thyroid glands after different doses of ^{131}I The three tables (A B C) collect the results from three different experimental series running at different times

Age of animals (days)	Inj ^{131}I (μCi)	$\bar{D}_{max}$ (rad)	Duration of PTU treatment (days)	No of animals	Body weight (g)	Thyroid weight (mg)	p
A							
140	—	—	—	19	32 3±0 5	3 95±0 10	
140	—	—	30	20	28 7±0 4	6 59±0 17	
140	0 60	1 900	30	20	29 1±0 2	6 56±0 16	—
140	1 5	4 700	30	20	29 3±0 6	5 90±0 20	<0 02
B							
119	—	—	14	20	27 3±0 7	5 77±0 27	
119	3 0	9 000	14	20	27 3±0 6	4 89±0 11	<0 01
130	—	—	—	20	31 3±0 4	3 64±0 21	
130	—	—	25	20	29 1±0 4	7 41±0 32	
130	3 0	9 000	25	20	28 1±0 4	5 51±0 15	<0 001
130	4 5	14 000	—	10	30 1±0 5	4 00±0 17	
C							
133	—	—	30	30	26 6±0 3	7 11±0 21	
133	1 5	4 700	30	36	25 8±0 3	7 04±0 13	—
133	2 1	6 600	30	10	30 6±0 4	5 93±0 23	<0 01

Table 4

Body and thyroid weights (±SE) in adult male mice with PTU treatment started 24 hours after injection of 1 5 and 2 1 μCi ^{131}I The animals were maintained on iodine deficient pellets during the entire course of the experiment P denotes the significance of the growth impairment

Age of animals (days)	Inj ^{131}I (μCi)	$\bar{D}_{max}$ (rad)	Duration of PTU treatment (days)	No of animals	Body weight (g)	Thyroid weight (mg)	p
119	—	—	30	20	26 6±0 4	8 84±0 31	
119	1 5	3 600	30	20	27 3±0 4	7 78±0 23	<0 01
119	2 1	5 000	30	20	26 0±0 4	5 80±0 22	<0 001

A tracer dose of ^{131}I was injected intraperitoneally one day before the litters were killed The 24-hour uptake gave *consistently* the same concentration of radioactivity in the thyroid gland, irrespective of the size of the earlier ^{131}I doses in other words, the uptakes were proportional to the thyroid wight *U* ı = 1 00±0 05 % of the *injected amount of radioactivity per mg of thyroid* tissue

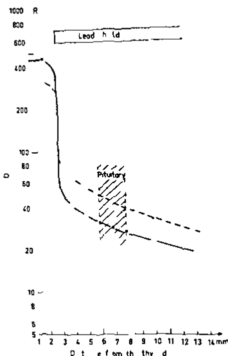


Fig 2 Roentgen dose to the neck and shielded parts of an adult mouse body The shaded area indicates the position of the pituitary gland in relation to the edge of the aperture of the lead shield The aperture was centered over the thyroid

Certain significant effects (thyroid growth inhibition and induction of adenomas) are however produced by roentgen irradiation of the thyroid in animals and human subjects at lower dose levels than those required to give rise to corresponding changes with ^{131}I (DONIACH 1963 UNSCEAR 1964) An important question that arises in this connection is why radiation with roentgen rays is so much more effective than radiation from ^{131}I to the thyroid This problem was therefore investigated in a number of roentgen experiments in mice Such experiments can obviously not be carried out in mouse foetuses so that the investigation was necessarily limited to a comparison of the inhibitory effect produced by the two types of radiation on goitrogen stimulated thyroid growth in adult mice

Irradiation procedure and dose calculations

The irradiation factors were 260 kV 10 mA filter 4 mm Al (inherent) + 0 85 mm Cu HVL 2 mm Cu focus — thyroid distance 23 cm giving a dose

PTU alone and in combination with injection of 1 5 μCi ^{131}I ($\bar{D}_{max} = 4\,000$ rad) The upper curve in Fig 1 *represents the thyroid growth after PTU* stimulation in mice maintained during the entire course of the experiment on an iodine deficient diet *containing 0 33 μg iodine per g pellet*

Discussion

Marked impairment of the normal growth of the thyroid gland in foetal and juvenile mice was evident after a maximum ^{131}I dose of 3 700 rad to its central parts This impairment of thyroid growth led to considerable histologic tissue changes (WALINDER 1972)

No histologically verifiable effects were present in the thyroid tissue of adult mice after 14 000 rad to the central part of the gland 39 days after the injection of ^{131}I It is possible, however, to produce a sensitivity to radiation of the adult thyroid gland similar to that observed in young animals by provoking growth of the gland with goitrogens Experimental results, not now reported, moreover indicate that mice following a dosage of 5 400 rad ^{131}I have thyroid weights at 1 5 years of age that are only half as great as those observed in unirradiated controls at the same age (WALINDER, unpublished)

These observations and the fact that the function (uptake of ^{131}I) of surviving cells appears to be unaffected by the doses used in the present investigation call for no further explanation of the difference in radiosensitivity of the normal adult and foetal mouse thyroid than the higher cell division rate of the latter This conclusion is corroborated by the observation made by a number of investigators that the growth impairment in a goitrogen challenged thyroid gland irradiated with ^{131}I is due to disturbance of the reproductive integrity of the epithelial cells *The increase in size of the cells does not seem to be affected to* any great degree (AL HINDAWI & WILSON 1965, DOBYNS et coll 1967, DONIACH & LOGOTHEOPOULOS 1955, *GREIG et coll 1965, MALOOF et coll 1952)*

Roentgen experiments

As mentioned in the introductory section fairly general agreement appears to exist today that roentgen irradiation of the cervical region in children increases the risk that malignancy will develop in the thyroid gland in later life The thyroids of these subjects seem in this respect to be more sensitive to radiation than those of adults (UNSCEAR 1964, DOLPHIN 1968) Although available data strongly indicate a correlation between roentgen irradiation over the neck region in infancy and later development of thyroid carcinoma there is a paucity of information concerning the corresponding effects of ^{131}I (cf DOLPHIN 1968)

Table 5

Body and thyroid weights in male mice irradiated with roentgen rays and challenged with PTU The time interval between the exposure to radiation and the PTU treatment was 14 days P denotes the significance of the growth impairment The animals in this table were 1 5 to 2 months older than those in the other experiments

Group	Age of animals (days)	Duration of PTU treatment (days)	No of animals	Body weight (g)	Thyroid weight (mg)	p
1	193	28	20		7 00 ± 0 39	< 0 01
2	193	28	30	28 0 ± 0 3	6 37 ± 0 24	< 0 001
3	193	28	40	28 9 ± 0 3	7 28 ± 0 15	0 01
4	193	-	10		5 2 ± 0 3	< 0 001
5	193		20	35 3 ± 0 5	5 0 ± 0 3	< 0 001
6	193	28	19		8 36 ± 0 22	

Table 6

Body and thyroid weights in male mice irradiated with roentgen rays and challenged with PTU The time interval between the injection of radioiodine and the start of PTU treatment was 24 hours

Group	Age of animals (days)	Duration of PTU treatment (days)	No of animals	Body weight (g)	Thyroid weight (g)	p
1	149	29	27	29 3 ± 0 4	7 76 ± 0 22	—
2	149	29	31	28 4 ± 0 3	6 64 ± 0 23	< 0 01
3	149	9	20	29 8 ± 0 6	7 75 ± 0 24	

Group 6 Unirradiated controls that had access to PTU water for the same length of time as the other animals

All the mice were males The housing and management of the mice was the same as in the ^{131}I experiments

An additional experimental series consisted of three groups of animals two of which were irradiated in the same way as in groups 1 and 2 in the preceding experiment but with 1 000 rad and a control group that received PTU in the water as in group 6 in the preceding experimental series

Results

Experiment 1 One day before the animals were killed 0 1 μCi ^{131}I was given to the mice in groups 4 and 5 The 24 hour uptakes were (percentage of injected amount ^{131}I ± standard error of the mean) 2 89 ± 0 15 per cent and 2 83 ± 0 20 per cent, respectively The mean thyroid weight in group 2 was significantly lower than that in group 3 ($p < 0 01$)



Fig 3 A roentgen irradiated mouse one month after exposure The unprotected skin under the aperture of the lead shield was badly damaged and the hair had lost its colour A sharp demarcation between this injured area and the shielded skin was evident

rate to the gland of 300 rad/min The mice were covered with 4 mm lead with an aperture over the neck region (including the thyroid gland) of 20 mm × 7 mm The animals were anaesthetized with Mebumal and placed with the back upwards towards the roentgen tube The trunk and head could thus be screened off from the radiation Special care was taken to avoid irradiation of the hypophysis, this was achieved by keeping the animal s head bent forward during the irradiation and by careful positioning of the aperture of the lead protector

The dose measurements were performed with films (Cine Positive 5302) placed above and below the neck of dead animals in the afore mentioned position under the aperture of the lead protector The relation between dose and film blackening was obtained by calibration of the film against a well calibrated thimble chamber coupled to a dosimeter (Philips Universal dosimeter 37470) The calibration was carried out under the aperture of the lead as well as below the lead itself In order to maintain the linear relation between dose and film blackening two exposures of different durations were necessary to evaluate the doses under the aperture and under the shielded parts of the film The dose in the hypophysis amounted to about 10 per cent of that to the thyroid (Fig 2) A ring of white hair around the animals necks was generally produced not long after the irradiation (Fig 3) The control mice were treated in exactly the same way as the experimental animals but were protected completely by lead

Two experimental series were set up, the first consisting of six groups of animals treated according to the following scheme All animals were maintained for 14 days before irradiation on an iodine deficient diet One day after irradiation this was changed to a diet with a high concentration of iodine

Group 1 1 500 rad in a single dose After 14 days, PTU was given in the drinking water (0 1 %) for 28 days

Group 2 1 500 rad in a single dose After 24 hours, PTU was administered as in group 1

Group 3 1 500 rad in three doses of 500 rad, 14 days, 7 days, and 1 day before a PTU challenge as in groups 1 and 2

Group 4 1 500 rad without PTU challenge

Group 5 *Unirradiated controls*

SUMMARY

The radiosensitivity of the goitrogen challenged thyroid gland was investigated in foetal and adult mice both after irradiation with ^{131}I accumulated in the gland and after roentgen radiation. The similar effect in the normally growing thyroid in the foetuses and young mice and the goitrogen stimulated adult animals suggested that the rate of thyroidal growth rather than the age of the mouse was the decisive factor in determining the degree of the reaction. Roentgen irradiation proved to be twice to four times more effective than radiation with ^{131}I.

ZUSAMMENFASSUNG

Die Strahlenempfindlichkeit der kropferzeugend behandelten Thyreoidea von fetalen und erwachsenen Mäusen wurde sowohl nach Bestrahlung durch ^{131}I angereichert in der Thyreoidea als auch nach Röntgenbestrahlung untersucht. Die Ähnlichkeit der Wirkung bei der normal wachsenden Thyreoidea der fetalen und jungen Maus und derjenigen beim erwachsenen kropferzeugend behandelten Tier deutet darauf hin, dass eher die Geschwindigkeit des Wachstums als das Alter der Maus der entscheidende Faktor ist, der die Grösse der Reaktion bestimmt. Röntgenbestrahlung erwies sich zwei- bis viermal effektiver als Bestrahlung mit ^{131}I.

RÉSUMÉ

La radiosensibilité de la glande thyroïde stimulée par un goitrogène a été étudiée sur des foetus de souris et sur des souris adultes après irradiation par ^{131}I fixé dans la glande et par irradiation par rayons de Roentgen. La similitude de l'effet sur la thyroïde en croissance normale des fœtus et des jeunes souris et sur la thyroïde des animaux adultes stimulée par un goitrogène fait penser que le facteur décisif qui détermine l'intensité de la réaction est plutôt le taux de croissance que l'âge des souris. L'irradiation par rayons de Roentgen a prouvé d'être deux à quatre fois plus effective que l'irradiation par ^{131}I.

REFERENCES

Al-Hindawi, A. Y. and Wilson, G. M. The effect of irradiation on the function and survival of rat thyroid cells. Clin. Sci. 28 (1965) 555.

Axelrad, A. A. and Leblond, C. P. Induction of thyroid tumours in rats by a low iodine diet. Cancer 8 (1955) 339.

Conard, R. A., Rall, J. D. and Sutow, W. W. Thyroid nodules as a late sequela of radioactive fallout in a Marshall island population exposed in 1954. New Engl. J. Med. 274 (1966) 1392.

Dobyns, B. M., Rudd, A. E. and Sanders, M. A. Desoxyribonucleic acid synthesis in the radiated and stimulated thyroid gland. Endocrinology 81 (1967) 1.

Dolphin, G. W. The risk of thyroid cancer following irradiation. Hlth Phys. 15 (1968) 219.

Doniach, I. Effects including cancerogenesis of ^{131}I and X rays on the thyroid of experimental animals. Hlth Phys. 9 (1963) 1357.

— and Logothetopoulos, J. H. Effects of radioactive iodine on the rat's thyroid function, regeneration and response to goitrogens. Brit. J. Cancer 9 (1955) 177.

Experiment 2 The effects of 1 000 rad roentgen irradiation on the PTU stimulated thyroidal growth are presented in Table 6 The goitrogenic challenge was significantly impaired by 1 000 rad roentgen irradiation, when administered 24 hours before the start of the PTU treatment If the time interval between the radiation exposure and the start of PTU treatment was increased to 14 days, the dose necessary for impairment of the goitrogenic challenge had to be increased to 1 500 rad (cf Table 5)

Comparative aspects of roentgen and ^{131}I irradiation

The *roentgen experiments* established that a dose delivered 24 hours before the PTU treatment produced a more marked effect than if the same dose was delivered 14 days before the start of the PTU stimulation or if the dose was fractionated over a period of 14 days prior to the PTU challenge This indicates that some recovery had taken place during the 14 days following the exposure, it also confirms the results of the ^{131}I experiments in which similar effects were obtained by reducing the time interval between the injection of the radioiodine and the PTU challenge from 14 days to 24 hours

Significant impairment of thyroid growth after 28 to 30 days treatment with PTU started 14 days after the roentgen exposure or the injection of ^{131}I necessitated a roentgen dose of 1 500 rad or an integrated ^{131}I dose of about 6 600 rad to the centre of the gland (the peripheral dose is then 2 600 rad according to WALINDER 1971) The corresponding dose values after reducing the time interval between exposure (injection) and the start of the PTU treatment to one day were 1 000 rad and about 1 600 to 4 000 rad (peripheral — central dose), respectively The 14 days' recovery thus implied a dose reduction factor of about 1 5, irrespective of the type of irradiation

The continuous (but decreasing) dose from ^{131}I necessary to produce a significant impairment of thyroid growth after PTU stimulation proved to be twice to four times higher than that required after three to five minutes of roentgen irradiation Fractionation of the roentgen dose as described did not imply a change of the radiation response as compared to that observed after a single exposure with the same dose 14 days prior to the growth stimulation The inhibitory effect of irradiation on thyroid growth produced by goitrogen in mice is thus obviously dependent on dose rate The skin changes observed in roentgen irradiated mice (Fig 3) demonstrated that roentgen doses of this magnitude produce considerable extrathyroidal damage Such an injury is, however probably of less importance in explaining the higher efficiency of roentgen as compared with ^{131}I irradiation than the difference in the dose rates (WALINDER et coll 1972)

FROM THE DEPARTMENT OF GYNECOLOGY (DIRECTOR: PROF. HANS LUDVIG KOTTMEIER), RADIUMHEMMET, THE DEPARTMENT OF SURGERY (DIRECTOR: PROF. CURT FRANKSSON), SERAFIMERLASARETTET, AND THE INSTITUTE OF TUMOR PATHOLOGY (DIRECTOR: PROF. JAN PONTÉN), KAROLINSKA SJUKHUSET, STOCKHOLM, SWEDEN

STENOSIS OF THE SMALL BOWEL AS A COMPLICATION IN RADIATION THERAPY OF CARCINOMA OF THE UTERINE CERVIX

by

INGEMAR JOELSSON, LARS RAF and GUNNAR SÖDERBERG

The adverse influence of radiation on the intestinal mucosa had been recognized before roentgen and gamma rays were first utilized in the therapy of malignant diseases. WALSH (1897) described a self-limiting condition of diarrhea and cramp ascribed at the time to thermal action. This could be prevented by placing metallic shields between the observer and the sources of radiation. As irradiation techniques became sophisticated and large doses of radiation were administered in each case, a certain frequency of intestinal reaction and damage became accepted as an inevitable consequence of the therapeutic modality. This applies especially to the treatment of carcinoma of the uterine cervix with the application of radioactive sources in the uterus and vagina: the most common site of reaction is the rectum, but the sigmoid colon, urinary bladder, small bowel, neck of the femur, and the skin are also liable to injury.

Compared with the frequency of 5 to 20 per cent for rectal complications induced during treatment of carcinoma of the uterine cervix (ANDERSON et coll. 1955, KOTTMEIER 1964 a, FRISCHBIER & LOHBECK 1970, JOELSSON 1970), the

This work was supported by grants from the Cancer Society of Stockholm and the King Gustaf V Jubilee Fund. Submitted for publication 22 December 1970.

— EADIE D G A and HOPE STONE H F The development of multiple thyroid adenomata in primary hyperthyroidism in previously irradiated thyroid glands Brit J Surg 53 (1966) 681
GOLDBERG R C, LINDSAY S, NICHOLS C W and CHAIKOFF I L Induction of neoplasms in thyroid gland of rats by subtotal thyroidectomy and by injection of one microcurie of ^{131}I Cancer Res 24 (1964) 35
GREIG W R CROOKS J and McGREGOR A G The radioprotective effect of methylthiouracil on the thyroid gland of the rat Brit J Radiol 38 (1965) 72
HEMPELMAN L H, PIFER J W, BURKE G J et coll Neoplasms in persons treated with X rays in infancy for thymic enlargement J nat Cancer Inst 38 (1967) 317
LINDSAY S and CHAIKOFF I L The effects of irradiation on the thyroid gland with particular *reference to the induction of thyroid neoplasms Cancer Res 24 (1964) 1099*
MALOOF F, DOBYNS B M and VICKERY A L The effect of various doses of radioactive iodine on the function and structure of the thyroid of the rat Endocrinology 50 (1952) 612
UNSCEAR A/AC 82/R 185/Add a 8 Feb 1964
WALINDER G Determination of the ^{131}I dose to the mouse thyroid Acta radiol Ther Phys Biol 10 (1971) 558
— Quantitative effects of ^{131}I on different tissue components in foetal and goitrogen challenged mouse thyroids To be published in Acta radiol Ther Phys Biol
— JONSSON C J and SJODEN A M Dose rate dependence in the goitrogen stimulated mouse thyroid To be published in Acta radiol Ther Phys Biol
WARREN S Pathological effects of thyroid irradiation A report of an advisory committee from the division of medical sciences National Research Council Washington D C *1966*

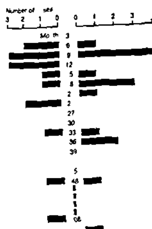


Fig 2 Distribution of cases according to interval between rad ation treatment and symptoms (left) and between radiation treatment and laparotomy because of ileus (right)

Results

A total of 6 154 cases of carcinoma of the cervix were examined at Radium hemmet during the period 1954—1969 with a view to treatment 3 075 of the e were living in the Stockholm area The rate of small bowel stenosis as a function of radiation therapy of carcinoma of the uterine cervix was accordingly 0 49 per cent a figure that is a non corrected and overall one

Five cases underwent radiation therapy in 1959 but the rest were evenly pread over the period 1958—1969 (Fig 1 a) Four of the ca es were operated upon for radiation stenosis in 1968 the rest being distributed over the eleven year period 1960—1970 (Fig 1 b) The interval between commencement of radiation therapy and laparotomy for ileus varied between 5 and 111 months (Fig 2) the mean value being 25 months The duration between the com mencement of symptoms and surgery was 0 to 7 months

The pre ence of adhe ions before radiation therapy has been suggested as a cau e of radiation damage to the mall intestine In the pre ent series laparotomy before radiation treatment had been carried out in 10 of the 15 cases Salpingo oophorectomy had been performed in 5 ca es (Table) Previous inflammatory di ea e in the pelvis or abdomen had occurred in 6 out of the 15 cases Two of them had a history of gonorrhea one of non specific acute alpingitis two of ap pendicitis and one of cholecystitis (Table)

Radiation technique Data for the details of the intracavitary and the external treatment were obtained for 14 cases the 15th case was in stage I and may have had intracavitary irradiation as the only and definitive mode of therapy Two additional cases in stage I received no external irradiation

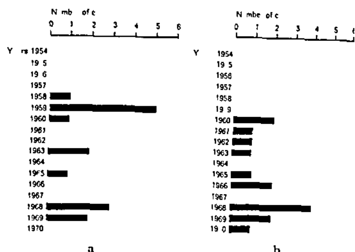


Fig 1 Distribution of cases according to year of commencement of radiation treatment (a) and year of surgery because of intestinal obstruction (b)

rate for complications of the small bowel ranges only between 0 5 and 5 per cent (ASHBAUG & OWENS 1963, KAPLAN 1956, SHAMBLIN et coll 1963, RUBIN & CASARETT 1968, GRAHAM & VILLALBA 1963)

The aim of the present paper is to report a series of cases, treated first by radiation therapy for carcinoma of the uterine cervix and later by surgery for verified radiation induced stenosis of the small bowel

Material and Methods The cases in the series were selected in the following two ways (1) A review was made of all cases treated for disease of the small bowel in any of the twelve departments of surgery in the Stockholm area during the period 1954—1968 inclusive The investigation was organized to ensure that as far as possible, the total number of such cases was registered (RAF 1967) The survey disclosed that during the 15 year period, approximately 3 000 cases had been operated upon for obstruction of the small bowel, non specific inflammatory obstruction without the characteristics of regional enteritis occurred in 125 cases Eighteen of these had a history of radiation treatment at Radiumhemmet for carcinoma of the uterine cervix Cases in which surgical specimens had not been taken (2 cases) or in which carcinoma had been present at operation (1 case) were immediately excluded and the specimens of the remainder were re examined by one of the authors (G S) Twelve cases fulfilled the criteria of having a history of radiation therapy and verification by microscopy of radiation induced injury to the small bowel (2) Three additional cases with radiation injury of the small bowel operated upon during the period January 1969 to March 1970, were subsequently included in the present series these were found in connection with a review of cases of carcinoma of the uterine cervix filed at Radiumhemmet

rad and a contribution to the bladder base and the anterior wall of the rectum of 600 to 1 300 rad. The pelvic dose distribution as a function of this technique has been reported by RANUDD (1966).

The external irradiation was in one case administered with ^{60}Co by two opposed beams with absorbers in both the anterior and the posterior beam to protect the central tissue volumes; the size of the fields was 250 cm² with SSD 60 cm. A parametrial dose of 4 500 rad was delivered in fractions of 300 rad (reference dose) six days per week, so that the contribution to the bladder base and to the anterior wall of the rectum was 1 500 rad.

One case received ^{60}Co external beam therapy with one 250 cm² anterior beam with a central shield and two opposed 125 cm² lateral beams with wedge filters SSD 60 cm. The parametrial dose was 4 000 rad with a weekly tumor dose of 800 rad and treatment fractions on 5 days per week. This irradiation contributed 2 000 rad to the bladder base and 2 800 rad to the anterior wall of the rectum. (Characteristics of the pelvic dose distribution of the respective ^{60}Co techniques were reported by KOTTMEIER 1964 b, RANUDD 1966 and JOELSSON 1970.)

Clinical course. The main symptom was usually intermittent attacks of abdominal colicky pain. A heavy meal seemed to induce an exacerbation so that the food intake was lowered and weight loss almost invariably reported as a consequence. Hemoglobin values below 10.8 g per cent were observed in one case and serum protein values below 6.8 per cent in 2 cases. The symptoms occurred directly following the completed course of radiation therapy in only 1 of the 15 cases, a free interval being present in the rest. Along with the aggravation of symptoms the signs were always those of intestinal obstruction. Roentgen examinations were performed in 10 cases in an attempt to establish this diagnosis and in 8 of these evidence of mechanical obstruction was obtained.

Resection of the stenotic part of the small intestine with end-to-end enteroanastomosis was performed in all except 3 cases in which the distal part of the ileum was resected together with the proximal part of the ascending colon; the resected segments measured 5 to 65 cm with a mean length of 30 cm. The presence of adhesion to the injured bowel was specifically noted in the report of 12 cases; in at least 7 of these the stenotic part of the bowel was firmly bound to the uterus but in the rest of the cases to the pouch of Douglas or the uterine tubes. The report of the operation gave no information concerning adhesions in 2 of the remaining cases but in the last case it was stated that no adhesions were present in the abdomen or pelvis.

A single stenosis 0.5 to 4 cm in length was evident in 14 cases. Two stenotic parts of the ileum were interconnected by approximately 80 cm of macroscopically normal intestine in the remaining case. A perforation of the small

Table

Proportion of cases with previous inflammatory disease or previous laparotomy

Previous inflammatory disease				Previous laparotomy			
Appendicitis	Cholecystitis	Gonorrhea	Salpingitis	Appendectomy	Cholecystectomy	Salpingo oophorectomy	Tubal ligation
2/15	1/15	2/15	1/15	2/15	1/15	5/15	2/15

The *intracavitary* part of the treatment was in 11 cases given according to the principles of the modified, individualized Stockholm technique. Regard was paid to the elasticity of the vagina, the type of the lesion, the extent of the growth and the position of the uterus. In cases of endocervical growth as well as in those in which the neoplasm had extended paracervically, the amount of radium in the intrauterine irradiator was increased (KOTTMEIER 1964 b). This was exemplified in 5 cases. From 43 to 150 mg radium were used in the uterus, and 60 to 144 mg of radium in the vagina. The treatment time varied between 20 and 25 hours per treatment course with two courses, 3 weeks apart.

The intracavitary irradiation was given in 4 cases with a remote afterloading technique that utilized applicators fixed to the patient by means of a corset. These carried activities 3.5 to 4 times larger than those in the modified, conventional Stockholm technique (WALSTAM 1965, JOELSSON & BACKSTROM 1970). From 159 to 209 mg of radium and 600 mCi cesium were used in the uterus and 600 mCi cesium in the vagina, respectively. The treatment times varied between 5 and 11 hours per course with two courses 3 weeks apart. The amount of irradiation was always indicated by the statement of dose of clinical significance, measured at the base of the bladder and the anterior wall of the rectum (GRAY & KOTTMEIER 1957, KOTTMEIER & GRAY 1961, JOELSSON & BACKSTROM 1969). The rectal dose from the intracavitary irradiation was below or about 4 000 rad varying between 2 500 and 3 800 rad in 12 of the 15 cases, in the rest it was 4 100 and 5 000 rad. The bladder dose was below 6 000 rad, varying between 2 650 and 5 800 rad in 13 of the cases, in one case it was 7 150 rad.

External beam therapy was administered in 10 cases with a medium energy roentgen technique with two abdominal and two gluteal fields or two opposing fields with central shielding blocks. The field areas ranged between 125 and 250 cm², FSD 50 to 75 cm, tube potential 170 to 200 kV and the filtration 0.5 mm Cu + 1 mm Al (HVL 1 mm Cu) or 0.44 mm Sn + 0.25 mm Cu + 1 mm Al (HVL 2 mm Cu) (THORAEUS 1932). A total of 6 × 400 R (in one case 10 × 300 R) over 4 to 6 weeks gave a parametrial dose of 1 200 to 2 600



Fig 4 Radiation injury of small intestine with fibrosis and deep fibrinoid necrosis under an ulcerated u face a) × 40 b) × 400

red in 3 ca es (Fig 4) Ulceration was eldom observed but changes in the epi thelium econdary to previous ulceration and inflammation with regeneration were often apparent

Inadequacy of the enteroanastomosis complicated the postoperative period in 4 ca es Ileocecal resection was performed in 2 of the e cases and ileocolos tomy without re ection in 1 case Resection with end to end enteroanastomo is was performed five weeks after the commencement of symptoms in the remaining case the patient died of peritonitis, with no evidence of carcinoma at autopsy

Symptoms and signs of intestinal obstruction were present postoperatively in 3 cases although the e did not nece sitate intervention An abscess in the abdomi nal scar occurred in 4 ca es The mean duration of stay in hospital after opera tion was 25 days

One patient died from complications in connection with the surgical procedure and one patient died 30 months after the laparotomy the cause of death being

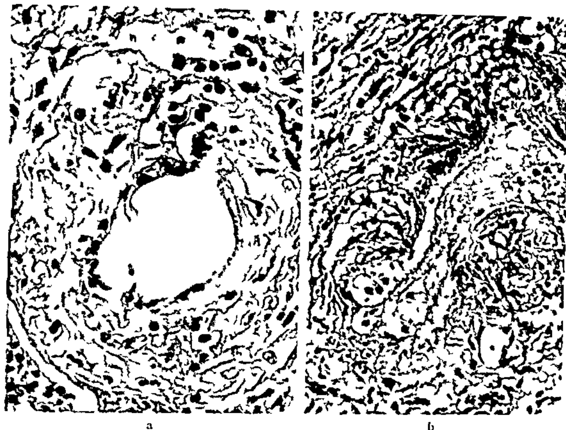


Fig 3 Dilated irregular capillary blood vessels with irradiation damage of fibrinoid type in the wall a) ×400 b) ×400

bowel proximal to the obstruction was either already present or was created in the dissection of adhesion in 3 cases, the bowel adjacent to the obstruction, especially proximally, was sometimes swollen and red but enlargement of mesenteric glands was only rarely evident The stenosis usually lay in the distal part of the ileum, the length of bowel between the stenosis and the ileocecal valve exceeded 100 cm in only 2 cases

The changes in the intestinal wall were always verified by *histologic* sections through the altered tissues Fibrosis of a more or less progressive type, with thick strands of insufficiently vascularized hyalinized connective tissue, replaced the muscularis to a lesser or greater extent the *sclerotic fibrous tissue* caused obstruction in most cases by circular constriction of the lumen Fibrinoid degeneration and necrosis, arising from damage to blood vessels, was often noted in the connective tissue The blood vessels were dilated (teleangiectatic) and irregular with degenerated walls (Fig 3) Deep fibrinoid necrosis with surrounding inflammatory reaction was present in 5 cases and perforation of the wall occur

of 71 cases with radiation injuries to the colon and small bowel that this interval averaged 13 months, but that in 4 per cent there was a delay of more than 10 years A few cases have al o been reported with an equally long time lag between the therapy and clinical signs in a smaller eries including radiation steno is only of the mall intestine (FRANK & POHLE 1951 GARDNER & ANIYAN 1952) Figures imilar to those ob erved in the material of Radiumhemmet eem to be widespread (WHITEY & SUGERBAKER 1950)

The overall rate of radiation induced obstruction of the mall bowel was 0 5 per cent in the present material The results indicate however that the in cidence of this complication to radiation therapy was higher during the last five years of the investigation period especially when allowance is made for the shorter ob ervation time of cases from this latter period Among 2 085 ca es treated with radiation therapy during the period 1954—1964 8 (0 3 per cent) developed radiation stenosis of the mall bowel while among those treated during 1965— 1969 7 out of 989 cases (0 7 per cent) had this equela

Pertinent to the influence of the intracavitary treatment and especially the distribution of radium is the ob ervation by KOTTMEIER (1953) that 2 756 patients treated for carcinoma of the cervix at Radiumhemmet from 1936 to 1945 had no complications of the mall bowel The radium was applied at the time according to the principles of the old Stockholm method and the doses given were comparatively small The 5 year apparent recovery rate was 42 5 per cent

The Stockholm technique after 1945 was changed considerably in the direction of individualization (KOTTMEIER 1964a) Suffice it to say that among everal factors the extent of the tumor was especially considered For example in ca es of endocervical malignant growth and in those with paracervical involvement an increa ed amount of radium was introduced into the uterine cavity and the cervix The observation had been made that the intrauterine radium was re pon ible for the larger proportion of the dose to the paracervical ti sue and the area of the regional lymph nodes After this change in the application technique the 5 year apparent recovery rate has markedly increa ed if ca es of endocervical carcinoma are considered the rate for stage I and IIa, which had been 57 per cent ro e to 81 per cent after the introduction of the individualized treatment method

The radium was evenly distributed in the cylindrical irradiator in the uterus from the beginning When however attention was focussed on the dose con tribution not only to the rectum and urinary bladder but al o to the sigmoid colon and mall bowel that often lay in close proximity to the uterine body the radium was redistributed in the intrauterine cylindrical irradiators with the admini tration of a lower do e to the fundus When the remote afterloading

ileus The latter had been free from signs of carcinoma at the last clinical examination, performed less than two months before death All the remaining patients are alive One of them has had diarrhea and occasional abdominal pain for 6 years after surgery Three of the patients had diarrhea as the only symptom for 8 to 10 months after the laparotomy One patient had sigmoid obstruction with abdominal distension and pain, which necessitated colostomy The remainders have been free from symptoms

Discussion

The pathogenesis of radiation enteritis has been described *in detail* by a great number of investigators (WARREN & FRIEDMAN 1942) The early radiation changes in the small bowel are edema and degeneration and necrosis of the epithelial cells of the mucosa Repair may be complete after an interval of weeks Edema and vascular damage with small hemorrhages occur in the submucosal and subserosal layers, and the lymphatic tissue in the injured part of the intestinal wall disappears

Endarteritis and fibrinoid degeneration of dilated blood vessels are evident in all layers of the intestinal wall in chronic processes Ulceration of the mucosa with deep necrosis sometimes develops and causes inflammation and fibrosis in the deeper layers Irradiation, however, may also selectively affect the connective tissue of the submucosa and cause an extensive fibrosis with hyalinization, thus a ring like band beneath an intact mucosa may contract centripetally and produce delayed intestinal obstruction

Investigations have elucidated that the small bowel is more sensitive to radiation than the colon (DESJARDINS 1931, ANDERSON et coll 1955) The fact that the frequency of complications of the small bowel despite this is low is generally ascribed to the motility of the small intestine When a radiation induced injury of the small bowel occurs, this part of the intestine has often been observed to be fixed to the uterus or its appendages by adhesions Subsequently, adhesions due to previous laparotomy or previous inflammatory disease increase the risk of small bowel complication (FRIEDMAN 1955, GRAHAM & VILLALBA 1963, POWEL SMITH 1965) In addition, the fact that in the present series the injured part of the small bowel was nearly always bound to the uterus and the adnexa makes it probable that the intracavitary rather than the external radiation treatment is incriminated as the cause of complication This contention is supported by the fact that the external irradiation had been given with medium energy roentgen techniques in all but two cases the *midpelvic doses being below* 1 300 rad

The interval *between the commencement of radiation therapy* and start of symptoms varies considerably FABRIKANT et coll (1959) reported in a series

of the intestine (0 5 to 4 cm) This made resection possible with the enteroanastomosis located in healthy tissue Such a situation might be encountered more often when the intracavitary part of the treatment is incriminated as in this series rather than when high energy external irradiation is the cause of the lesion The limited extent of injury of the intestine encountered in this series may also be an explanation for the good long term results after intestinal resection Despite an observation period of several years signs of serious obstruction have not developed

SUMMARY

Radiation induced injury of the small bowel was observed in 15 of 3 075 cases from the Stockholm area treated for carcinoma of the uterine cervix during the 16-year period 1954—1969 Factors that might increase the risk of this complication are discussed Symptoms and signs of the intestinal complications are described and the results of surgical treatment presented

ZUSAMMENFASSUNG

Strahleninduzierte Schaden des Dunndarms wurden bei 15 von 3 075 Fallen des Stockholmer Gebietes die wegen eines Carcinoms des Cervix uteri wahrend der 16 Jahres Periode 1954—1969 behandelt worden waren beobachtet Faktoren die das Risiko fur diese Komplikationen steigern mogen werden besprochen Die Symptome und Zeichen der intestinalen Komplikationen werden beschrieben und die Resultate der chirurgischen Behandlung dargestellt

RÉSUMÉ

Sur 3 075 cas de cancer du col uterin traites pendant une periode de 16 ans de 1954 a 1969 dans le district de Stockholm les auteurs ont observe 15 cas de radiolesions de l'intestin grele Ils etudient les facteurs qui pourraient augmenter le risque de cette complication Ils decrivent les signes fonctionnels et les signes physiques de ces complications intestinales et presentent les resultats du traitement chirurgical

REFERENCES

ANDERSON R E WITKOWSKI L J and PONTIUS G V Radiation stricture of the small intestine Surgery 8 (1955) 605

ASHBAUGH D G and OWENS J C Intestinal complications following irradiation for gynecologic cancer Arch Surg 87 (1963) 116

DESJARDINS A U Action of roentgen rays and radium on the gastrointestinal tract experimental data and clinical radiotherapy Amer J Roentgenol 26 (1931) 145

FABRIKANT J I ANLYAN W G and CREADICK R N The management of radiation injuries to the intestines Sth med J 52 (1959) 1186

FRANK R C and POHLE E A Late radiation reaction in the small intestine manifest eight years after therapy Ann Surg 133 (1951) 104

FRIEDMAN N B Pathogenesis of intestinal ulcers following irradiation effects of colostomies and adhesions Arch Path 59 (1955) 2

system was first employed in clinical routine (WALSTAM 1965), an *intrauterine* applicator loaded with 160 to 210 mg radium was used, a capsule of low activity being placed in the fundus. Later, when [137] Cs replaced radium, the loading of 600 mCi was divided among six sources of equal activity.

The present investigation elucidates that in 7 of 13 cases *radium irradiators and in 2 cases* cesium irradiators of high activity had been introduced into the uterus, other factors might have contributed to causing a high, local dose of radiation to an intestinal loop of *limited length in the remaining cases*. The radiation therapy had been immediately preceded by *salpingo-oophorectomy* in 2 cases and in one case by pelvic inflammation, a perforation of the uterus was moreover probable at the first radium treatment in one of these cases. Abundant pelvic adhesions were present at operation in the 3 cases. In one case local *infection with discharge* had occurred in between the radium applications as a sign of local infection, while in the last case no cause for the complication was *apparent and the operation report recorded no pelvic adhesions*.

Although acute radiation gastro-intestinal injury may be fulminant, it either spontaneously resolves or progresses only slowly to symptoms. Chronic radiation disease presents with anorexia, weight loss, diarrhea, vomiting and intermittent intestinal obstruction. The hematocrit and albumin levels are often both low and it is questionable whether the hypoalbuminemia is secondary to a lesion of the wall of the small intestine or is a function of the decreased food intake (VATISTAS & HORNSEY 1966). *Such malnutrition is probably more* common in intestinal damage due to external radiation therapy, where long segments of small bowel may be involved. Severe malnutrition resulting in hypoproteinemia was uncommon in this series of short intestinal stenoses.

Roentgenographic examination of the intestine may disclose puddling of barium in the terminal part of the ileum, with a bulbous appearance and segmental saw-tooth strictures. A rigid intestine with destruction of the mucosal *folds, often similar to that in regional enteritis*, may also be observed. A barium examination of the small bowel is necessary to localize stenosis but signs of obstruction are usually evident in conventional films. The roentgen examination had given the correct diagnosis in most cases of the present series.

It is recognized that the risk of postoperative complications is markedly increased after surgery in the irradiated region in patients with previous radiation therapy, a complication at the site of the intestinal anastomosis with fistula formation is therefore not unusual. This has also been the experience in the present series in which 4 of 15 cases had this sequela. Surgical removal of the damaged part of the intestine was however followed by the absence of further major signs in the rest of the series. It is suggested that the explanation of this good result of surgical intervention is the limited length of the damaged segment

QUANTITATIVE AND QUALITATIVE ASPECTS OF RADIOBIOLOGY AND THEIR SIGNIFICANCE IN RADIATION THERAPY

by

R WIDEROE

The importance of radiobiologic investigations in radiation therapy has always been recognized Until recently however the influence on therapy of most mainly morphologic research has been fairly small and restricted to more or less vague confirmation of clinical experiences New experimental quantitative work in radiobiology (as developed since 1950) has changed the situation markedly (PUCK & MARCUS 1956) Survival curves of mammalian cells measured on irradiated cell cultures in vitro are now discussed by radiotherapists (GAUWERKY 1965 trying to find a base for improved treatment schemes as well as better evaluation of the various types of radiation (roentgen rays , rays electrons neutrons and negative pions etc) today available for tumor therapy

Theoretic considerations have enlightened more or less obscure concepts such as RBE (radiobiologic efficiency) and OER (oxygen enhancement ratio) but knowledge on conditions in vivo primary cell reactions and cell kinetics is still limited It must be remembered that quantitative experiments in vitro often are restricted to the ability of cells to produce clones (of a certain size) *in a* specified medium whereas the survival of cells in vivo may be essentially different

Submitted for publication 9 March 1970

FRISCHBIER H J und LOHBECK H U Behandlungsergebnisse und Komplikationen bei der Megavolttherapie des Carcinoma Colli Uteri Strahlentherapie 140 (1970), 13
GARDNER C E and ANLYAN W G Radiation injury to the small intestine Surgery 31 (1952) 746
GRAHAM J B and VILLALBA R J Damage to the small intestine by radiotherapy Surg Gynec Obstet 116 (1963) 566
GRAY M J and KOTTMEIER H L Rectal and bladder injuries following radium therapy for carcinoma of the cervix at the Radiumhemmet Amer J Obstet Gynec 74 (1957) 1294
JOELSSON I Radiotherapy of carcinoma of the uterine cervix with special regard to external irradiation Acta radiol (1970) Suppl No 302
— and BACKSTROM A Dose rate measurements in bladder and rectum Intracavitary radiation of carcinoma of the uterine cervix Acta radiol Ther Phys Biol 8 (1969) 343
— — Applicators for remote afterloading technique for optimum pelvic dose distribution in carcinoma of the uterine cervix Acta radiol Ther Phys Biol 9 (1970) 233
KAPLAN B J Some clinical aspects of factitial proctitis A report of 62 cases Conn med J 20 (1956) 357
KOTTMEIER H L Carcinoma of the female genitalia The Abraham Flexner Lectures No 11 Baltimore 1953
— (a) Complications following radiation therapy in carcinoma of the cervix and their treatment Amer J Obstet Gynec 88 (1964) 854
— (b) Erfahrungen des Radiumhemmet in Stockholm mit Hochvolttherapie beim Collumcarcinom Arch Gynak 202 (1964) 305
— and GRAY M J Rectal and bladder injuries in relation to radiation dosage in carcinoma of the cervix Amer J Obstet Gynec 82 (1961) 74
POWELL SMITH C Factors influencing the incidence of radiation injury in cancer of the cervix J Canad Ass Radiol 14 (1965) 132
RAF L Enteric coated potassium chloride tablets and ulcers of the small intestine Acta chir scand (1967) Suppl No 374
RANUDD N F Dose distribution studies in external irradiation of carcinoma colli uteri Acta radiol Ther Phys Biol 4 (1966) 353
ROSEN I B and SHAPIRO B J Radiation enteropathy of the small bowel Canad med Ass J 91 (1964) 681
RUBIN P H and CASARETT G W Clinical radiation pathology Vol I W B Saunders Philadelphia 1968
SHAMBLIN J R SYMMONDS R E SAUER W C and CHILDS D S Bowel obstruction after pelvic and abdominal radiation therapy Factitial enteritis or recurrent malignancy Ann Surg 160 (1963) 81
THORAEUS R A study of the ionization method for measuring the intensity and absorbtion of roentgen rays and of the efficiency of different filters used in therapy Acta radiol (1932) Suppl No 15
WALSH D Deep tissue traumatism from roentgen ray exposure Brit med J 2 (1897) 272
WALSTAM R Studies on therapeutic short distance and intracavitary gamma beam techniques Acta radiol (1965) Suppl No 236
WARREN S and FRIEDMAN N B Pathology and pathologic diagnosis of radiation lesions of the intestinal tract Amer J Path 18 (1942) 499
VATISTAS S and HORNSEY S Radiation induced protein loss into the gastro intestinal tract Brit J Radiol 39 (1966) 547
WILEY H M and SUGARBAKER E D Roentgenotherapeutic changes in the small intestine — surgical aspects Cancer 3 (1950) 629

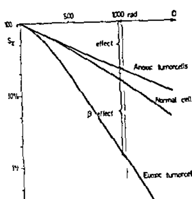


Fig 2 Typical shape of survival curves for euoxic and anoxic tumor cells as well as normal cell irradiated in vivo with low LET radiation ($\alpha = 0.10$) Parameters $D_{\alpha 0} = 66$ rad $D_\beta = 213$ rad and 640 rad (normal cells) $p = 4$ Semilogarithmic display

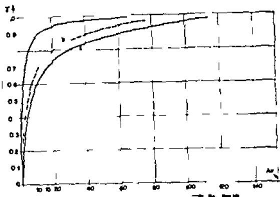


Fig 3 The dose modifying factor γ as a function of oxygen pressure in the surroundings for various biologic objects Curve a Ehrlich ascites tumor cells (DESCHNER & GRAY) Curve b Germinative cells of growing bone in mouse tail (HOWARD FLANDERS & ALPER) Curve c Human kidney cells (T1) in cell cultures (BARENDSEN)

This equation is closely connected to a simplified model for ionizing radiation the two-component theory (WIDERØE 1966 1968) This theory assumes radiation to be composed of two parts a high linear energy transfer (LET) part the α component and a low LET part the β component The dose part of the first is αD whereas the β component being the rest of the dose is $(1-\alpha) D$ The value of α is different for various types of radiation from 6 to 8 % for high energy electrons to nearly 100 % for 4 MeV α rays for 200 keV roentgen radiation the value is about 0 16 Eq (1) indicates that the resulting cell survival is the product of two different and independent cell reactions

$$S_\Sigma = S_\alpha S_\beta \tag{2}$$

where $S_\alpha = e^{-\alpha D/D_{\alpha 0}}$ is the result of a dose proportional cell killing (a one hit reaction) whereas $S_\beta = 1-(1-e^{-(1-\alpha)D/D_{\beta 0}})^p$ signifies a non linear effect of the dose (a multi target reaction) It is postulated (and this so far is the only hypothesis) that these two cell reactions are caused by the α and the β components of radiation respectively In a semilogarithmic display the α effect will give a straight line through zero for the cell survivals and the β effect a shoulder curve (Fig 2) For large doses we obtain

$$S_\Sigma = p\, e^{-D/D_0} \tag{3}$$

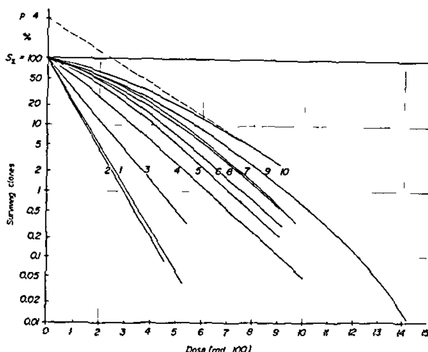


Fig 1 Effects of different types of radiation on the capacity for clone formation by human kidney cells (From BARENDSEN 1964) 1 — Alpha particles from Po 210 (3.4 MeV 140 keV/μ of tissue) $a = 0.98$ 2 — Cyclotron accelerated alpha particles (5.2 MeV 85.8 keV/μ of tissue) $a = 1.0$ 3 — Cyclotron accelerated alpha particles (8.3 MeV 60.8 keV/μ of tissue) $a = 0.69$ 4 — Cyclotron accelerated alpha particles (26.8 MeV 24.6 keV/μ of tissue) $a = 0.43$ 5 — Cyclotron accelerated deuterons (3.45 MeV 17.4 keV/μ of tissue) $a = 0.33$ 6 — Cyclotron accelerated deuterons (6.3 MeV 11.0 keV/μ of tissue) $a = 0.285$ 7 — Cyclotron accelerated deuterons (14.87 MeV 5.6 keV/μ of tissue) 8 — 20 keV roentgen rays (average LET about 6 keV/μ of tissue) $a = 0.21$ 9 — 200 keV roentgen rays (average LET about 2.5 keV/μ of tissue) $a = 0.16$ 10 — Beta particles from ^{90}Y ($E_{\beta max} = 2.2$ MeV average LET about 0.3 keV/μ of tissue) $a = 0.09$

(ALPER 1961, RUBIN & CASARETT 1968) The limitation of quantitative counting to cell survivals only neglects the qualitative radiation effects that are essential to the understanding of the cell reactions, thus seriously restricting the value of such measurements to clinical radiology (GARTNER 1961)

Cell survival curves Fig 1 indicates the cell survival for cultures of human kidney cells (T1) irradiated with various types of radiation (BARENDSEN 1964) These and similar survival curves may be described mathematically by eq (1) where S_x is the resulting cell survival and D the applied dose

$$S_x = e^{-D/D_{\alpha_0}}\left[1-\left(1-e^{-(1-\alpha)D/D_{\beta_0}}\right)^p\right] \qquad (1)$$

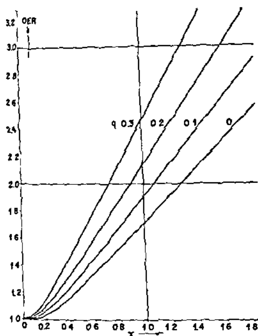


Fig 4 Oxygen enhancement ratio for 10 survivals (OER) as a function of the dose modifying factor for various values of q Parameters $\alpha =$ 0 16 200 keV roentgen rays $D_{\alpha o} =$ 66 rad $D_{\beta o} \sim 213$ rad $p \sim 4$

Influence of oxygenation on radiation sensitivity REVESZ & LITTBRAND (1964 1966) as well as other investigators have observed that for truly anoxic cells the α effect is nearly unchanged whereas the β effect will be completely suppressed The β effect is only partly suppressed for incomplete anoxia The survivals due to the β effect may be described by eq (4) where is a function of the oxygen pressure (Fig 3)

$$S_\beta = 1 - \left(1 - e^{\frac{-(1-\alpha)\gamma \ D}{D_\beta}}\right)^p \qquad (4)$$

The α effect may indeed also be slightly influenced by oxygen pressure as indicated by eq (5) where q is the reduction in the α value for complete anoxia

$$S = e^{-\alpha(1-q(1-\gamma))D/D_o} \qquad (5)$$

Measurements as yet are diverging but a reduction in the α value to about 70 % for complete anoxia (i e $q = 0\ 3$) seems probable (WIDEROE 1970) This reduction is often insignificant and may be neglected Fig 4 presents OER_{10} values as a function of γ for various values of q The value of $q = 0\ 3$ suits experimental results with 200 keV roentgen radiation very well Fig 5 demonstrates cell survival curves for $\gamma = 1$ (aerobic cells) $\gamma = 0\ 5$ and $\gamma = 0$ (anoxic cells)

With

$$D_o = \frac{D_{\beta o}}{1+\alpha(D_{\beta}/D_{\alpha o}-1)}$$

which is a tangent to the survival curve at $S_x = 0$ (infinite dose) This tangent will cut the ordinate axis at a point p, designated as the extrapolation number The parameters derived from the survival curves of the human kidney cells in Fig 1 are

$$p = 4,\ D \ = 66 \text{ rad } D_{\beta} = 213 \text{ rad}$$

with α values from 0 09 (curve 10) to 1 0 (curve 2) The α values may be correlated to the mean LET values for various radiations but a determination based on the biologic α and β effects is often preferable The α values of Fig 1 can be related to the average LET values (L) by the equation,

$\alpha = \sqrt{L/100\text{keV}/\mu}$

The RBE values for various types of radiation and for different values of cell survival may easily be calculated by means of eq (1) The fact often mentioned that RBE (and also OER) depends on the cell survival value would suggest a standardization to certain fixed values, for instance $S_x = 0\ 50$ (RBE_{50}), or $S_x = 0\ 10$ (RBE_{10}), to avoid misunderstanding Human kidney cells are not very sensitive to radiation The parameters fitting the curves in Fig 1 give a D_0 value of 158 rad for 200 keV roentgen radiation D_0 values between 100 and 150 rad have been recorded for other cell types REVESZ & LITTBRAND (1967) have measured values of $D_{\alpha o} = 38$ R, $D_{\beta} = 111$ R and $D_0 = 91$ R (190 keV roentgen rays) for ELD ascites tumor cells The radiation sensitivity changes during the cell cycle and most values given refer to an asynchronous cell population of an average distribution

SINCLAIR (1967) irradiated synchronized Chinese hamster lung cells (subline V 79 285 B) with 250 keV roentgen radiation and reported that the late S phase was most resistant With $\alpha = 0\ 16$ the parameters were

$$D_{\alpha o} = 109 \text{ rad } D_{\beta o} = 310 \text{ rad } D_o = 245 \text{ rad}$$

During the other parts of the cell cycle the α sensitivity of the cells changes drastically, increasing fivefold for the mitose phase ($D \ = 21\ 2$ rad) which represents a pure α effect ($D_{\beta} = \infty$) The α sensitivity in the G_2 phase is slightly lower ($D_{\alpha o} = 25\ 3$ rad) and after mitosis gradually decreases through the G_1 phase ($D_{\alpha o} = 35$ rad) and early S phase ($D_{\alpha} = 48\ 5$ rad) to the lowest value with $D_{\alpha o} = 109$ rad The α sensitivity thus seems to reflect post and premitotic activity during the cell cycle culminating in the mitoses The β effect remains constant and is of less importance

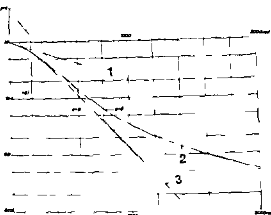


Fig 6 Cell survivals for a mixed population containing 10 completely anoxic cells Curve 1 S for euoxic cells Curve 2 S_F for anoxic cells Curve 3 Asympthotic tangents for euoxic cell survivals Parameters $\alpha = 0\ 10$ $D_{\infty} = 66$ rad $D_{\beta_0} = 213$ rad $p = 4$ The curves indicate the survivals for $\alpha = 0$ and 0 10

I Early death also characterized as interphase death the first period intracellular direct effect or primary reaction chiefly covers a succession of nuclear cell reactions that cause destruction of the nucleus (lysis) and consequently the death of the cell (FLIEDNER & STADTMEISTER 1962) One of the first signs is nuclear pyknoses and certain alterations in the nucleus The nuclear volume often increases because of an oedematic liquid and the chromatin is displaced and approaches the nuclear membrane The nucleolus is enlarged with alterations the nuclear membrane also presenting structural alterations (PARCHWITZ 1957)

A strong extrusion of nuclear substances DNA and RNA from the nucleus to the cytoplasm may be evident and the concentration of RNA in the plasma increases Later on destroyed parts of nuclei may be observed between the cells (WENDT 1959)

It seems that early death is mainly caused by a metabolic disorganization of the nuclear matrix thus causing alterations and disturbances in DNA and RNA production and possibly also damage to the DNA constitution (TAHMISIAN 1961) When such damage exceeds the nuclear and cytoplasmic repair capacity the nucleus disintegrates and early death of the cell occurs (HARTWEG 1963) The cytoplasm also presents alterations The mitochondria elongate and approach the nuclear membrane the membrane system of the ergastoplasm enlarges and the protein synthesis increases Highly differentiated and matured cells are much less vulnerable than strongly proliferating cells, obviously the nuclear information through DNA and RNA molecules is less important in such cases The nuclear destruction and early death seem to be mainly an α reaction which only to a small extent can be influenced by extracellular factors The structural

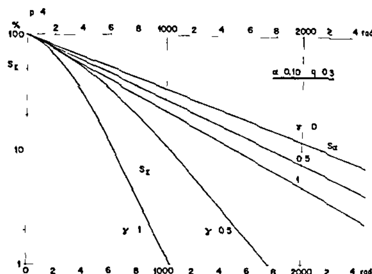


Fig. 5. Cell survival curves for γ = 1, 0.5 and 0 for $a = 0.10$ with $q = 0.3$. Parameters $D_0 = 66$ rad, $Dp_0 = 213$ rad, $p = 4$.

for $a = 0.10$ and $q = 0.3$. The differences in the S values due to a 30% reduction in the a effect are so small that they often cannot be measured.

The extrapolation number p in the equations remains unchanged when the oxygen pressure is reduced. This is easy to understand because the tangent to the survival curve is drawn to a point in infinity ($S_\Sigma = 0$, $D = \infty$). Tangents drawn to finite points on the curve with $S_\Sigma > 0$ will cut the ordinate axis at points lower than p (NEARY 1968). Such apparent extrapolation numbers are the values usually reported by experimental investigators. The apparent value for complete anoxia will be 1.

If a relative part, a, of a cell population is completely anoxic the equation of cell survival (assuming $q = 0$) will be

$$S_\Sigma = e^{-aD/D_0}\,[1-(1-a)(1-e^{-(1-a)D/Dp_0})^p] \qquad (6)$$

as in Fig. 6. The population after large doses will mainly consist of anoxic cells.

Cellular radiation effects. When cells are irradiated with high doses exceeding 50 to 100 krad, various cell components are so severely damaged that they become completely denaturated (lysis) thus causing acute cell death. The doses for radiation therapy are usually much smaller and here the phenomenon is therefore without interest. The effects following therapeutic doses (mostly below 1 000 rad) have been classified as (PARCHWITZ 1963): (1) early death covering an interval mainly less than 10 h after irradiation, (2) mitosis stop: the mitosis rate is either reduced or blocked for a certain time, and (3) delayed death which may occur after a few cell divisions producing abnormal and defective daughter cell

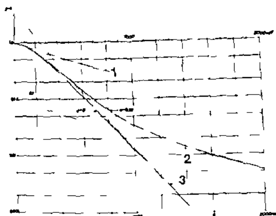


Fig 6 Cell survivals for a mi ed population containing 10 com pletely anoxic cells Curve 1 S for euoxic cells Curve 2 Sr for anoxic cells Curve 3 Asympthotic tangents for euox c cell survivals Parameters $a = 0\ 10$ D_{oo} 66 rad $D_{\beta o} = 213$ rad $p = 4$ The curves ind cate the survivals for $a = 0$ and 0 10

1 *Early death* al o characterized as interpha e death the first period intracellular direct effect or primary reaction chiefly covers a succession of nuclear cell reactions that cause destruction of the nucleus (lysis) and conse quently the death of the cell (FLIEDNER & STADTMEISTER 1962) One of the first signs is nuclear pykno es and certain alterations in the nucleus The nuclear volume often increases becau e of an oedematic liquid and the chromatin is displaced and approaches the nuclear membrane The nucleolus is enlarged with alterations the nuclear membrane al o presenting structural alterations (PARCHWITZ 1957)

A strong extru ion of nuclear substances DNA and RNA from the nucleus to the cytopla m may be evident and the concentration of RNA in the pla ma increases Later on destroyed parts of nuclei may be observed between the cells (WENDT 1959)

It eems that early death is mainly caused by a metabolic di organization of the nuclear matrix thus causing alterations and disturbances in DNA and RNA production and po sibly al o damage to the DNA constitution (TAHMISIAN 1961) When such damage exceeds the nuclear and cytopla mic repair capacity the nucleus disintegrates and early death of the cell occurs (HARTWEG 1963) The cytopla m also presents alterations The mitochondria elongate and approach the nuclear membrane the membrane system of the ergastopla m enlarges and the protein synthe is increa es Highly differentiated and matured cells are much less vulnerable than strongly proliferating cells obviou ly the nuclear information through DNA and RNA molecules is less important in such ca es The nuclear destruction and early death seem to be mainly an a reaction which only to a mall extent can be influenced by extracellular factors The structural

organization of the nucleus is probably of a 'one track' type leading to one hit reactions instead of cytoplasmic damage where many parallel structures may be doing the same work (MAZIA 1961) Radiation of the nucleus with UV micro beams also leads to a typical a reaction (VON BORSTEL & MOSER 1955) During mitosis (as well as in the G_2 phase) when the chromosomes and the mitotic apparatus are highly active, the nucleus is especially vulnerable (in a certain case more than five times compared with the late S phase) to a damage (GRUNDMANN 1952, HARBERS 1962)

The modest influence of oxygenation on the a effect may be explained not only by a different distribution of oxygen in the cytoplasm and nucleus but also by primary effects leading to structural damage being less oxygen dependent in the nucleus (SCHJEIDE et coll 1956)

2 *Delayed cell division Mitosis stop* This is one of the earlier and more sensitive reactions observed in the cell With small doses the mitosis rate becomes reduced, for larger doses mitoses are completely blocked and the duration of the stop often increases proportionally with the dose (FRITZ NIGGLI 1959, GARTNER 1963) The disturbance of the mitosis cycle may have different causes, such as chromosome defects, defects in the structure and kinetics of the chromosomes and alterations in the structural matrix of the nucleus and nucleolus (GAULDEN & PERRY 1958) To these must be added changes in the DNA structure as well as damage to the cytoplasm where the production of enzymes and membranes may have been disturbed (SCHERER 1963, CARLSON 1954) DNA and RNA productions proceed independently of the mitosis delay (GARTNER 1963)

Observations seem to indicate that the cell and particularly the cytoplasm shortly after irradiation are mainly occupied with reparation of radiation damage and this task precludes any cell division (DURYEE 1949), such division can for instance proceed only after the endosplasmatic reticulum has been repaired (PARCHWITZ 1963, BRAUN & KAWAMURA 1964) This may explain the fact that division delay increases with the dose It seems that this constitutes a simple method of studying repair processes in the cell and it is regrettable that so little quantitative information exists on this phenomenon (NYGAARD 1962, LESHER & BAUMAN 1968)

3 *Delayed death (mitotic linked death)* The discrimination between cells undergoing early and delayed death may sometimes be difficult However, it is often possible to observe the appearance of early death cells which reach a maximum value after a few hours and then gradually disappear before the cells with delayed death begin to appear, chiefly together with mitotically connected abnormalities (FLIEDNER et coll 1961) (Fig 7)

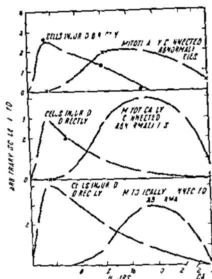


Fig 7 Ri e and decay of directly injured cells and mitotically connected abnormal cells after whole body irradiation of rats with 500 1 000 and 5 500 R (From FLIEDNER et coll)

Severely damaged cells often try to divide but fail and are eliminated Observations of alterations in the cytoplasm and nucleus show reactions obviously different from early death signs (GARTNER 1963) Delayed death appears mostly to be connected with degeneration and destruction of the cytoplasm Changes with reductions and more or less complete lysis without new creations of christae appear in the mitochondria The same is al o true for the ergastoplasm where the membranes dissolve and large vacuoles and cavities appear this structure eems to be more ensitive than the mitochondria (PARCHWITZ 1963) The nucleus also alters and behaves quite differently An important point is that no nuclear substances are being transferred in this pha e from the nucleolus to the cytopla m These substances accumulate especially in the nucleolus where great alterations occur in the nucleus where the production of DNA and RNA is still taking place This together with the mitosis blockage is the rea on for the production of abnormal giant cells (GARTNER 1963) The reduction of DNA and RNA concentrations in the cytoplasm will inhibit the albumin and protein production and thus render repair work more difficult It is however remarkable that non lethal damage can be repaired completely during a relatively short period of 6 to 12 hours (Elkind recovery) This indicats that the recovery of the cytopla m as long as the capacity is not exceeded is rapid Sublethal damage of the crypt cells of the small intestine may for instance be repaired in ten minutes

All this strongly suggests that the delayed cytopla mic death must be identical with the β effect evident in the survival curves Investigations of cytopla mic

organization of the nucleus is probably of a 'one track' type leading to one hit reactions instead of cytoplasmic damage where many parallel structures may be doing the same work (MAZIA 1961) Radiation of the nucleus with UV microbeams also leads to a typical *a* reaction (VON BORSTEL & MOSER 1955) During mitosis (as well as in the G_2 phase) when the chromosomes and the mitotic apparatus are highly active, the nucleus is especially vulnerable (in a certain case more than five times compared with the late *S* phase) to *a* damage (GRUNDMANN 1952, HARBERS 1962)

The modest influence of oxygenation on the *a* effect may be explained not only by a different distribution of oxygen in the cytoplasm and nucleus but also by primary effects leading to structural damage being less oxygen dependent in the nucleus (SCHJEIDE et coll 1966)

2 *Delayed cell division Mitosis stop* This is one of the earlier and more sensitive reactions observed in the cell With small doses the mitosis rate become reduced, for larger doses mitoses are completely blocked and the duration of the stop often increases proportionally with the dose (FRITZ-NIGGLI 1959, GARTNER 1963) The disturbance of the mitosis cycle may have different causes, such as chromosome defects, defects in the structure and kinetics of the chromosomes and alterations in the structural matrix of the nucleus and nucleolus (GAULDEN & PERRY 1958) To these must be added changes in the DNA structure as well as damage to the cytoplasm where the production of enzymes and membranes may have been disturbed (SCHERER 1963, CARLSON 1954) DNA and RNA productions proceed independently of the mitosis delay (GARTNER 1963)

Observations seem to indicate that the cell and particularly the cytoplasm shortly after irradiation are mainly occupied with reparation of radiation damage and this task precludes any cell division (DURYEE 1949), such division can for instance proceed only after the endosplasmatic reticulum has been repaired (PAPCHWITZ 1963, BRAUN & KAWAMURA 1964) This may explain the fact that division delay increases with the dose It seems that this constitutes a simple method of studying repair processes in the cell and it is regrettable that so little quantitative information exists on this phenomenon (NYGAARD 1962 LESHER & BAUMAN 1968)

3 *Delayed death (mitotic linked death)* The discrimination between cells undergoing early and delayed death may sometimes be difficult However, it is often possible to observe the appearance of early death cells which reach a maximum value after a few hours and then gradually disappear before the cells with delayed death begin to appear chiefly together with mitotically connected abnormalities (FLIEDNER et coll 1961) (Fig 7)

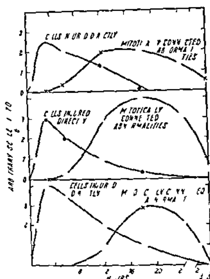


Fig 7 Rise and decay of directly injured cells and mitotically connected abnormal cells after whole body irradiation of rats with 500 1 000 and 5 500 R (From FLIEDNER et coll)

Severely damaged cells often try to divide but fail and are eliminated Observations of alterations in the cytoplasm and nucleus show reactions obviously different from early death signs (GARTNER 1963) Delayed death appears mostly to be connected with degeneration and destruction of the cytoplasm Changes with reductions and more or less complete lysis without new creations of christae appear in the mitochondria The same is also true for the ergastoplasm where the membranes dissolve and large vacuoles and cavities appear this structure seems to be more sensitive than the mitochondria (PARCHWITZ 1963) The nucleus also alters and behaves quite differently An important point is that no nuclear substances are being transferred in this phase from the nucleolus to the cytoplasm These substances accumulate especially in the nucleolus where great alterations occur in the nucleus where the production of DNA and RNA is still taking place This together with the mitosis blockage is the reason for the production of abnormal giant cells (GARTNER 1963) The reduction of DNA and RNA concentrations in the cytoplasm will inhibit the albumin and protein production and thus render repair work more difficult It is however remarkable that non lethal damage can be repaired completely during a relatively short period of 6 to 12 hours (Elkind recovery) This indicats that the recovery of the cytoplasm as long as the capacity is not exceeded is rapid Sublethal damage of the crypt cells of the small intestine may for instance be repaired in ten minutes

All this strongly suggests that the delayed cytoplasmic death must be identical with the β effect evident in the survival curves Investigations of cytoplasmic

organization of the nucleus is probably of a "one track" type leading to "one hit" reactions instead of cytoplasmic damage where many parallel structures may be doing the same work (MAZIA 1961). Radiation of the nucleus with UV micro beams also leads to a typical α reaction (VON BORSTEL & MOSER 1955). During mitosis (as well as in the G_2 phase) when the chromosomes and the mitotic apparatus are highly active, the nucleus is especially vulnerable (in a certain case more than five times compared with the late S phase) to α damage (GRUNDMANN 1952, HARBERS 1962).

The modest influence of oxygenation on the α effect may be explained not only by a different distribution of oxygen in the cytoplasm and nucleus but also by primary effects leading to structural damage being less oxygen dependent in the nucleus (SCHJEIDE et coll. 1956).

2. *Delayed cell division. Mitosis stop.* This is one of the earlier and more sensitive reactions observed in the cell. With small doses the mitosis rate becomes reduced, for larger doses mitoses are completely blocked and the duration of the stop often increases proportionally with the dose (FRITZ NIGGLI 1959, GARTNER 1963). The disturbance of the mitosis cycle may have different causes such as chromosome defects, defects in the structure and kinetics of the chromosomes and alterations in the structural matrix of the nucleus and nucleolus (GAULDEN & PERRY 1958). To these must be added changes in the DNA structure as well as damage to the cytoplasm where the production of enzymes and membranes may have been disturbed (SCHERER 1963, CARLSON 1954). DNA and RNA productions proceed independently of the mitosis delay (GARTNER 1963).

Observations seem to indicate that the cell and particularly the cytoplasm shortly after irradiation are mainly occupied with reparation of radiation damage and this task precludes any cell division (DURYEE 1949); such division can for instance proceed only after the endosplasmatic reticulum has been repaired (PARCHWITZ 1963, BRAUN & KAWAMURA 1964). This may explain the fact that division delay increases with the dose. It seems that this constitutes a simple method of studying repair processes in the cell and it is regrettable that so little quantitative information exists on this phenomenon (NYGAARD 1962, LESHER & BAUMAN 1968).

3. *Delayed death (mitotic linked death).* The discrimination between cell undergoing early and delayed death may sometimes be difficult. However, it is often possible to observe the appearance of early death cells which reach a maximum value after a few hours and then gradually disappear before the cells with delayed death begin to appear, chiefly together with mitotically connected abnormalities (FLIEDNER et coll. 1961) (Fig. 7).

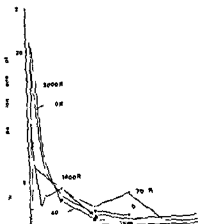


Fig 8 Number of dead cells (early death) recorded per section of one crypt after whole body irradiation of mouse with doses from 700 to 2 400 R (From DEVIK)

after doses of 1 500 R could a weight reduction of 10 % in the irradiated part (half of the kidney was screened with lead) be observed after three months and only few histologic alterations (variations in nuclear dimensions with polymorphic nuclei) were evident According to the survival curves for human kidney cells (BARENDSEN 1964) (Fig 1) the survival after 1 500 R should be 0 05 % and even the α effect alone should destroy 97 % of all cells

Observations in vivo indicate that cytoplasmic damage prevails even in mitoses when the sensitivity of the nucleus is at a maximum (most kidney cells are non proliferating) it is less than that of the cytoplasm Measurements in vitro on proliferating cell cultures therefore seem to be of little value for estimating damage in vivo to human organs with functional cells even allowing for fairly wide differences between human and rat cells

DEVIK (1971) administered whole body irradiation to male and female albino mice of the WLO strain and (after killing the animals) investigated the effects on the epithelial cells in the crypts of the small intestine These cells are strongly proliferous and known to possess high radiation sensitivity WITHERS & ELKIND (1969) used an in vivo method devised by TILL & MCCULLOCH (1963) to count visible nodules of mucosal epithelium that had developed in the crypts 13 days after local irradiation to the small intestine They recorded a D_0 of about 98 rad with a high value for the extrapolation number (about 100) indicating a high capacity for sublethal repair Similar values for D_0 varying between 80 and 190 rad have been reported for other cell types (bone marrow, spleen cells etc) by different investigators (PHILLIPS & HANKS 1968) with the same or similar in vivo methods Normal extrapolation numbers suit the survival values measured in these cases

reactions under anoxia may confirm this hypothesis The fact that cytoplasmi functions, and consequently repair of damage as well, can be stimulated extra cellularly by hormones is important Several observations indicate that even lethally β damaged cells may be recovered by extracellular humoral factor (BENJAMIN & YOST 1960) This may be different for various cell types

Radiation therapy The aim of radiation therapy is to reduce cells in mostly deep-seated tumors to a small number, perhaps below 10^{8} or 10^{9} Single doses are therefore repeatedly administered to the tumor volume and its surroundings This leads to a problem The tissue of the surroundings are populated with normal cells (stroma) that have to replace the vanishing tumor and therefore the normal cell population should not excessively or permanently be damaged The problem can of course be solved only if some electivity between normal cells and tumor cells exists or can be established Here the different cell reactions to the two radiation components may be important The sensitivity to the α component might possibly be more or less equal for both cell types, however, the β effect offering possibilities for extra cellularly stimulated repair can be very different for normal and neoplastic cells where the humoral influence is small (WIDEROE 1966, 1969) An increase in the electivity therefore demands treatment schemes that favour the β effect as much as possible This means (1) use of a low LET radiation with a low α value such as produced by high energy electrons (2) administration of as high single doses as can be tolerated because of damage caused to normal cells in the tumor bed

The great importance of the radiation program is thus obvious, to a high degree it is determined by the reactions of proliferous and functional normal cells To avoid inflammation, fibrosis or an impairment of the vascular system the radiation damage caused by the single dose should as far as possible be repaired in the resting interval between irradiation (RUBIN & CASARETT 1968) This means that the damage caused should not exceed a certain safe amount which may be specific for various types of tissue The situation therefore calls for investigation of cell kinetics counting the disappearance of denaturated cells, recognizing the delay of mitoses and watching the repopulation of the tissue with new viable cells Tissue regeneration is a complicated process starting with maturating and differentiation of surviving competent stem cells that develop into functional cells The relative part of stem cells and their rate of proliferation should be known The homeostatic mechanisms that balance the sequence of proliferation, differentiation and cell compensation governing the dynamics of regeneration are practically unknown (PATT 1968)

Normal tissue reactions in vivo FEINE (1963) investigated the radiation effects on rat kidneys with single doses of 500 1 000, 1 500 and 2 000 R Only

Table

Various treatment schemes

	Electrons	Cobalt 60 γ rays	200 keV rtg rays	High energy neutrons	
=	8	12	16	40	
D	250 rad	250 rad	250 rad	200 rad	Orthodox
D_{total}	10 500 rad	8 100 rad	6 800 rad	3 250 rad	treatment
n	42	32 5	27 3	16 2	schemes
Interval (t)	1 day	1 day	1 day	3 5 days	26 36 4(
t_{total}	41 days	32 days	27 days	54 days	and 70
Total repopulation	1 100	1 200	1 250	1 160	(neutrons) repopulation
Weekly repopulation	184	258	320	142	after each irradiation
Conversion for a=0 10=const	17	15 8	14	3	
D	920 rad	630 rad	490 rad	200 rad	Proposed
D_{total}	6 300 rad	5 800 rad	5 400 rad	3 250 rad	high intensity
n	6 8	9 2	11	16 2	treatment
t	7 days	4 days	4 days	3 5 days	schemes
t_{total}	43 days	33 days	40 days	54 days	70 repopu
Total repopulation	490	650	830	1 160	lation of normal cells
Weekly repopulation	70	123	132	142	after each irradiation
Conversion for a=0 10=const	83	67	48	3	

$D_{\omega\omega}$ = 66 rad $D_{\beta 0}$ = k 213 rad p = 4 k = 1 for tumor and 5 for normal cells End point = = 1 4 10 tumor cells

lation methods with parameters chosen from clinical experience may therefore be used as a first approximation For lung tissues an assumed reduction of normal cells to 30 % mainly by α effects (assuming $D_{\alpha\alpha} = 66$ rad $D_{\beta_0} = 1\,065$ rad and $D_0 = 482$ rad for $\alpha = 0\,08$) will give values for the highest allowable single doses in close agreement with clinical findings (WIDEROE 1969) A week seems ample for the recovery time after such doses (about 900 to 1 000 rad for high energy electrons)

Various treatment schemes calculated with the assumption that the surviving normal cells are reduced to 30 % after each single dose the end point of the

DEVIK counted dead crypt cells with pyknotic nuclei (early death) at various time intervals after irradiation with 700 to 2 000 R (Fig 8) As already described the dead cells appear shortly after irradiation, their number reaching a maximum after about 3 hours and when they slowly decay Assuming *e* functions for the appearance and decay of the cells, the time constant for the first is about 1 16 hours, for the decay about 12 hours and the total number of cells destroyed about 1 45 times the maximum count at 3 hours The result gave a total destruction of about 48 5 % of the crypt cells after a dose of 1 000 R, corresponding to a D_0 value of 245 R or 230 rad This is very different from that indicated by the measurements of WITHERS & ELKIND and it highlights the divergent results produced by the present methods

Measurements of the number of living cells in the crypts (delayed death candidates, defective daughter cells and repopulation from survivors) are also not in agreement with the cell losses by irradiation and cell migration to the villi

Observations of radiation effects on lung tissue constitute a third example BASSLER & BUCHWALD (1966) irradiated the lungs of 60 Sprague Dawley rats with 2 000 R (skin dose, 250 keV, 88 R/min) and described early radiation reactions Two hours after the irradiation some lymphocytes and reticulum cells had evidence of nuclear destruction with pyknosis and nuclear debris However, the lymphoreticular tissues recovered so that the reaction did not appear to be significant Of greater importance was an increase in the capillary permeability of the endothelium and alveolar lining associated with septal and intracellular oedema Exudation of plasma into connective tissue was accompanied by hyperaemia and interstitial inflammation which gradually developed into progressive fibrosis The alterations in the 100 Å thick cell membranes of the endothelial cells appeared to be the initial as well as the lasting effects of importance Alveolo capillary membrane swelling and ruptures could also be observed The air blood distance increased Similar reactions have also been recorded in irradiated human lungs

All observations seem to indicate that cell destruction is of less importance compared to functional damage and alterations in lung tissue and its regeneration It should be mentioned that vascular damage to the capillary system, causing alterations in permeability, thickening of the walls and circulation disturbances (hyperaemia), is a common phenomenon which may frequently restrict the magnitude of the applied single doses

The result of these few examples does not appear encouraging for a quantitative analysis Necessary information on normal tissue cell reactions is still far away (GARTNER 1961) However, there is no doubt that such reaction follow more or less similar patterns as revealed by cell cultures in vitro The same calcu

values from 38 to 215 rad were recorded The average value for the most common class of metastases was $D_\infty = 66$ rad, the same value as for human kidney cell in vitro Highly differentiated tumor cells are usually resistant whereas strongly proliferating cells are very sensitive, BREUR observed that the doubling time for lung metastases was inversely proportional to the radiation sensitivity The differences in sensitivity between various neoplasms possibly depend on the tissue in which the primary tumor has started

Carcinoma of the upper parts of the trachea is extremely sensitive to the α effect while in other tumor types the β effect seems more important However, the relative importance of the two reactions depends markedly on the magnitude of the dose given and so often in the reports the dose has not been specified Irradiation of the Walker carcinoma in the rat causes an 18 hour mitosis stop with a dose in the therapeutic range (PARCHWITZ 1963 BROWN & BERRY 1968)

The stroma consisting of connective tissue and vascular systems is of considerable importance to the sensitivity of tumor cells (LELBACH 1965) This is probably mainly a result of the oxygen concentration which much influences the β effect

Most tumors contain necrotic poorly vascularized parts and regions where the cells live under anoxic conditions Such anoxic cells are of importance in the destruction of the tumor they may after certain doses of irradiation constitute the greater part of the surviving cells (Fig 6) A single dose of 920 rad high energy electrons will reduce the number of well oxygenated tumor cells to about 2 7 % if the same radiation sensitivity as for the human kidney cells in Fig 1 is presumed With 10 % anoxic cells however the survivals would be 5 7 % more than twice as high and the relative anoxic cells would have increased to 58 % (LALA 1968)

The findings of VAN PUTTEN & KALLMAN (1966) on KHT sarcoma of C3HK mice are important and must be mentioned These authors reported that due to changed conditions of vascularization during fractionated radiation a substantial part of the anoxic cells is supplied with oxygen and thus made more sensitive to radiation This phenomenon of reoxygenation has also been confirmed by THOMLINSON (1967) and EMERY inter alios for human tumors It means that the relative part of the anoxic cells may remain nearly constant during a fractionated treatment if sufficiently high single doses are given RUBIN (1967) and RHEINHOLD (1967) have investigated the increase in vascularization in neoplasms during treatment When the malignant cells are denaturated and the remnants carried away the internal tumor pressure due to such cells that are growing disappears and the capillary system extends thus increasing the blood supply and oxygenation of the cells The conditions for this to happen are then

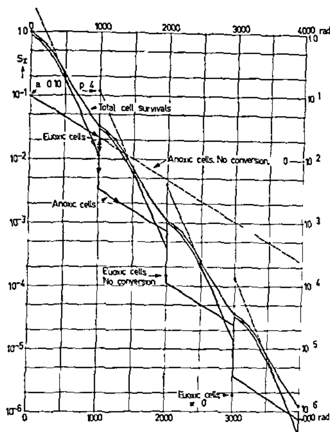


Fig 9 Idealized survival for cells in a tumor with 90 % euoxic and 10 % anoxic cells During the interval between irradiations 85 % of the remaining anoxic cells are converted to euoxic cells thus keeping the percentage of anoxic tumor cells constant at 10 % during treatment Parameters α = 0 10 D_o = 66 rad $D_{\beta o}$ = 213 rad ρ = 4 a = 0 10 = constant conversion rate $\varkappa$ = 84 8 %

tumor cell reduction being 1 4 × 10^9, are grouped in the Table The total repopulation of normal cells may be regarded as a measure of the radiation burden inflicted during the treatment This burden is the smallest for high single doses of high energy electrons (about 490 %) and much greater for high LET radiations, such as high energy neutrons (1 160 %)

Tumor cell reactions Cytologic investigations indicate that the radiation reactions on tumor cells are not different from the effects previously described (RAUSCH 1967) Measurement of survivals in vitro (aerobic conditions) indicate for HeLa cells sensitivity parameters of D_{oo} ~ 66 rad, $D_{\beta o}$ ~ 160 to 220 rad Values of D_{oo} ~ 66 rad $D_{\beta o}$ = 190 rad have been measured for lymphocytic leukemia cells (DBA/2 JN mice) whereas REVESZ & LITTBRAND (1967) recorded D = 36 rad, D_β = 104 rad (BROWN & BERRY 1968) for ELD ascites tumor cells (Chinese hamsters)

BREUR (1966) investigating human lung metastases in vivo (lung metastases can be regarded as a cell culture of a pure cell line in vivo) reported that the growth and radiation sensitivity of such tumors may differ considerably D

and in the future negative pions as well may here be mentioned. The treatment method proposed and practiced years ago by BACLESSE (1958) who employed many small single doses extended over a fairly long time was based on α effects only and could therefore be of advantage (VAN PUTTEN 1968).

Conclusions

Attempts to apply quantitative findings in radiobiology to the radiation therapy of tumors have been described. Some results of cell survival measurements on cell cultures in vitro are presented and mathematical descriptions based on the two component theory of radiation given. This also includes the influence of oxygen concentration on cell sensitivity. However, such investigations may represent an oversimplification and neglect the importance of different cell reactions. Some important cell reactions have been described and it is suggested that early death reactions may be identical with α effects whereas delayed death corresponds to the β effect.

This has important bearings on radiation therapy because the β effect may present a greater difference (selectivity) between normal and tumor cells than the α effect. This could explain the success of high energy electron therapy with fairly large single doses and longer intervals between irradiations (LOERBROKS & SCHUMACHER 1965). Descriptions of three experiments with irradiated animals where tissue reactions in vivo have been investigated indicate marked discrepancies in measurements of cell cultures and observations on cell survivals in vivo (method of counting surviving cell nodules after local irradiation). Obviously such measurements are today in a preliminary stage only. This might also be true of knowledge on the reactions on irradiated tumors. Great differences in sensitivity have been observed; however, it seems that cell destruction is not so very far removed from reactions observed in cell cultures. Anoxic tumor cells represent a problem which, however, seems often to be solved by the process of reoxygenation. When this does not work satisfactorily (EICHHORN 1969) anoxic tumor cells may preferably be destroyed by radiations having a large α component such as high energy neutrons or (in the future) negative pions. The method of BACLESSE (1958) in which the many small single doses avoid β effects might also be used.

SUMMARY

The survival of mammalian cells in proliferating cell cultures exposed to various types of radiation is described and analyzed mathematically. Such investigations neglect the influence of *milieu* and different qualitative cell reactions. The results should therefore not be transferred *indiscriminately* to clinical treatment. However, general directions for treatment schemes *using* various types of radiation can be determined and cell parameters chosen that correspond well to present clinical experience.

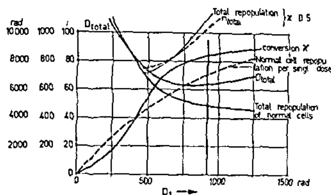


Fig 10 Repopulation of normal cells (tumor bed) after each irradiation total repopulation of normal cells during treatment total dose and conversion rate after each session are displayed as a function of the single dose The percentage of anoxic cells is assumed to be constant (10 %) during treatment Parameters $a = 0.10$ $a = 0.08$ (electron therapy) $D_{\omega o} = 66$ rad $D_{\beta} = 213$ rad (tumor cells) and 1 065 rad (normal cells) $p = 4$ End point is $1.4 \cdot 10^{9}$ tumor cells

(1) single doses must be high enough for a substantial part of the tumor cells to be destroyed, (2) the dose must not be so high as to damage the vascular system (i e below 1 000 rad), (3) the time interval between irradiations must be sufficient for the extension of the vascular system

Fig 9 presents survival curves for fractionated irradiation (single doses are 1 000 rad) of a neoplasm with 10 % anoxic cells When this relative part has to remain constant a conversion rate of about 85 % for the anoxic cells is necessary More anoxic cells are then eliminated by conversion than by direct radiation effects thus clearly demonstrating the importance of this process in tumor destruction

Little information concerning possible conversion rates for different types of tumors exists today Fig 10 displays the necessary conversion rates as well as total repopulation of normal cells in the tumor bed as functions of single high energy electron doses It is evident that single doses should be lowered when the conversion rate is smaller and the relative part of anoxic cells is to be kept constant during treatment Thus the effectivity of the conversion process may impose another limitation upon the magnitude of the most suitable single doses to be used If, for instance, the conversion rate is only 50 %, the single doses should not exceed about 500 rad, bringing the total repopulation of the normal cells to about 700 % if the number of tumor cells is to be reduced to 1.4×10^{9} The possibility cannot however be excluded that reoxygenation may sometimes not work or act only insufficiently EICHHORN (1969) has described observations on irradiated human lung neoplasms removed surgically after irradiation Even after treatment with high single doses this author sometimes observed viable anoxic tumor cells firmly embedded in fibrous tissue, the remaining malignant cells might however perhaps be unable to proliferate and thus cause a recurrence A further reduction in such anoxic cells might therefore justify treatment with high LET radiations having high a effects Irradiations with high energy neutrons

graphic (H^3 thymidine) changes in bone marrow following total body irradiation Amer J Path 38 (1961) 599
— und STADTMEISTER R Experimentelle und klinische Strahlenhamatologie J F Lehman Munchen 1962
FRITZ NIGGLI H Strahlenbiologie Grundlagen und Ergebnisse Thieme Verlag Stuttgart 1959
GARTNER H Experimentalforschung an Gewebekulturen als Grundlage fur die Behandlung mit energiereichen Strahlen Strahlentherapie 114 (1961) 1
— Untersuchungen an der Gewebekultur *In* Strahlenpathologie der Zelle S 85 Herausgegeben von E Scherer und H S Stender Thieme Verlag Stuttgart 1963
GAULDEN M E and PERRY R P Influence of the nucleolus on mitosis as revealed by ultraviolet microbeam irradiation Proc nat Acad Sci 44 (1958) 553
GAUWERKY F Klinische biologische und physikalische Gesichtspunkte fur die Erarbeitung eines Bestrahlungsplanes Sonderbande zur Strahlentherapie Band 61 B S 191 Urban und Schwarzenberg Munchen 1965
GRUNDMANN E *Karyologische und karyometrische Untersuchungen an Lymphknotenpunktatur bei Stickstoff Lost Therapie* Z ges exp Med 118 (1952) 489
HARBERS E Wirkungen ionisierender Strahlen auf die Zelle Dtsch med Wschr 87 (1962) *1395*
HARTWEG H *Strahlenwirkungen auf Zellen wichtiger Organe Blutbildendes Gewebe In* Strahlenpathologie der Zelle S 129 Thieme Verlag Stuttgart 1963
LALA P K Cytokinetic control mechanisms in Ehrlich ascites tumour growth *In* Effects of radiation on cellular proliferation and differentiation p 463 International Atomic Energy Agency Vienna 1968
LELBACH W K Histologische Veranderungen an bestrahlten Karzinomen *In* Grundlagen und Praxis der Bewegungsbestrahlung Herausgegeben von W Girardet Janker Verlag Wuppertal Elberfeld 1955
LESHER S and BAUMAN J Recovery of reproductive activity and the maintenance of structural integrity in the intestinal epithelium of the mouse after single-dose whole body ^{60}Co gamma ray exposures *In* Effects of radiation on cellular proliferation and differentiation International Atomic Energy Agency Vienna 1968
LOERBROKS B und SCHUMACHER W Behandlungsergebnisse und intrathorakale Strahlenreaktionen bei der Therapie des Bronchuscarcinoms mit schnellen Elektronen Beitr Klin Tuberk 131 (1965) 131
MAZIA D Mitosis and the physiology of cell division *In* The Cell Vol III Edited by J Brachet and A E Mirsky Academic Press New York London 1961
NEARY G J The dependence of the biological effectiveness of radiation on physical factors of radiation quality and the significance of such dependence Proceedings of the symposium on microdosimetry *Ispra 1967 Edited by H G Ebert European Communities Brussels* 1968
NYGAARD O F Effects on radiation on nucleic acid concepts *In* The effects of ionizing radiation on immune processes Gordon and Breach New York 1962
PARCHWITZ H K *Strahlenwirkung auf Tumorzellen In* Strahlenpathologie der Zelle S 334 Herausgegeben von E Scherer und H S Stender Thieme Verlag Stuttgart 1963
PATT H M Radiobiology of cell renewal *In* Effects of radiation on cellular proliferation and differentiation p 3 International Atomic Energy Agency Vienna 1968
PHILLIPS T L and HANKS G E Apparent absence of recovery in endogeneous colony forming cells after irradiation under hypoxic conditions Radiat Res 33 (1968) 517
PUCK T T and MARCUS Ph J Action of X rays in mammalian cells J exp Med 103 (1965) 653

ZUSAMMENFASSUNG

Das Überleben von Säugetierzellen in proliferierenden Zellkulturen, die verschiedenen Typen von Strahlung ausgesetzt wurden, wird beschrieben und mathematisch analysiert. Derartige Untersuchungen vernachlässigen den Milieueinfluss und verschiedene qualitative Zellreaktionen. Die Ergebnisse sollten deshalb *nicht kritiklos* auf die klinische Behandlung übertragen werden. *Allgemeine Angaben über Behandlungsschemen* für verschiedene Strahlentypen können jedoch aufgestellt und die Zellparameter so gewählt werden, dass sich eine gute Übereinstimmung mit der heutigen klinischen Erfahrung ergibt.

RÉSUMÉ

L'auteur décrit et analyse mathématiquement *la survie de cellules de mammifères* dans des cultures cellulaires proliférantes exposées à divers types de radiation. Ces recherches ne tiennent pas compte de l'influence du milieu et des différentes réactions cellulaires qualitatives. *Des données générales concernant les schémas de traitement pour les divers genres de radiations peuvent cependant être énoncées*; de même on peut choisir les paramètres cellulaires de telle façon qu'une corrélation soit assurée avec *les résultats cliniques actuels*.

REFERENCES

ALPER T.: Effects on subcellular units and freeliving cells. *In*: Mechanisms in Radiology VI. Edited by M. Errera and A. Forssberg. Academic Press, New York 1961.

BACLESSE F.: Clinical experience with ultra fractionated roentgen therapy. *In*: Progress in radiation therapy, Vol. 1, p. 128. Edited by F. Buschke. Grune and Stratton, New York 1958.

BARENDSEN G. W.: Mammalian cytogenetics and related problems in radiobiology. Pergamon Press, London 1964.

BÄSSLER R. und BUCHWALD W.: Experimentelle Entzündung und Fibrose des Lungengerüstes durch ionisierende Strahlen. Fortschr. Röntgenstr. 104 (1966), 192.

BENJAMIN T. L. and YOST H. T.: The mechanism of uncoupling of oxidative phosphorylating in rat spleen and liver mitochondria after whole body irradiation. Radiat. Res. 12 (1960), 613.

BRAUN H. und KAWAMURA I.: Die Substruktur von Tumorzellen nach Röntgenbestrahlung. Naturwissenschaften 51 (1964), 108.

BREUR K.: Growth rate and radiosensitivity of human tumours I and II. Europ. J. Cancer 2 (1966), 157.

CARLSON J. G.: Immediate effects on division, morphology and viability of the cell. *In*: Radiation biology. Edited by A. Hollaender. McGraw Hill Book Comp., New York, Toronto, London 1954.

DEVIK F.: Intestinal cell kinetics in irradiated mice. A quantitative investigation of the acute reaction to whole body roentgen irradiation. Acta radiol. Ther. Phys. Biol. 10 (1971), 129.

DURYEE W. R.: The nature of radiation injury to amphibian cell nuclei. J. nat. Cancer Inst. 10 (1949), 735.

EICHHORN H. J., LESSEL A. und JACOB R.: Der Einfluss unterschiedlicher Einzeldosen und Fraktionierung-Rhythmen auf die Rückbildung menschlicher Tumoren (Histologische Untersuchung). Strahlentherapie 140 (1970), 148.

FEINE U.: Niere. *In*: Strahlenpathologie der Zelle, S. 277. Herausgegeben von E. Scherer und H. S. Stender. Thieme Verlag, Stuttgart 1963.

FLIEDNER T. M., BOND V. P. and CRONKITE E. P.: Structural, cytological and autoradio

FROM THE DEPARTMENT OF RADIOLOGY CENTRE FRANÇOIS BACLESSE (DIRECTOR J S ABBATUCCI) CAEN, FRANCE

A TENTATIVE ANALYSIS OF THE INFLUENCE OF THE TIME FACTOR IN 192 IRIDIUM TREATMENT

by

J ROBILLARD, J E COUETTE P GAZENGEL J BLOQUEL and F LARRA

Although the influence of time in radiation therapy has long been investigated (REGAUD 1913) and owing mainly to ELLIS (1967 1968) considerable progress has recently been made in clinical dosimetry by the so called N S D notion the present advances in treatment have been confined to discontinuous external radiation therapy (FOWLER et coll 1963 1966 1968 1970) The aim of the present authors has been a tentative clinical evaluation of the influence of the time factor in curietherapy

Material and Method The series consisted of 151 cases in which all such locations were excluded where mucosal reactions could not be observed as for instance the uterus and the lower part of the tongue Only needles wires and moulded in apparatus were used The distribution was as follows 109 patients treated with needles 26 with wires and 16 with moulded in apparatus Of the many intervening factors in the reactions of the skin and mucosa the following were chosen (1) the typical criteria of the reactions (2) the occasional association with discontinuous external radiation therapy (cobalt), (3) the instruments in use (4) the dose at the hull (the hull being the isodose line

Submitted for publication 2 November 1970

RAUSCH L Anwendung strahlenbiologischer Erkenntnisse in der Strahlentherapie aus der Sicht des experimenteltatigen Strahlenbiologen Sonderbande zur Strahlentherapie Band 64 B S 24 Urban und Schwarzenberg Munchen 1967

REVESZ L and LITTBRAND B Variation of the relative sensitivity of closely related neoplastic cell lines irradiated in culture in the presence or absence of oxygen Nature 203 (1964) 742

— — Qualitative differences between cellular radiation damage suffered under oxic and anoxic conditions *the dual effect of oxygen Proc Intern* Conference on Radiation Biology and Cancer, Kyoto 1966 p 67 Radiation Society of Japan 1967

RHEINHOLD H S The postirradiated behaviour of transplantable solid tumors in relation to the regional oxygenation *In* Progress in radiology p 1482 Int Congress Series No 105 Excerpta Medica Foundation Amsterdam 1967

RUBIN P The clinical implications of the supervascularization effect of irradiated regressing tumors Atmospheric vs hyperbaric oxygen breathing *In* Progress in radiology II p 1487 Int Congress Series No 105 Excerpta Medica Foundation Amsterdam 1967

— and CASARETT G W *Clinical radiation pathology*, W B *Saunders Philadelphia 1968*

SCHERER F und STENDER H S Die Erscheinungsformen des zellularen Strahlenschadens Schlussbetrachtung *In* Strahlenpathologie der Zelle S 364 Herausgegeben von E Scherer und H S Stender Thieme Verlag Stuttgart 1963

SCHJEIDE O A MEAD J F and MYERS JR L S Notions on sensitivity of cells to radiation Science 123 (1956) 1020

SINCLAIR W K Radiation effects on mammalian cell populations in vitro *In* Radiation research p 607 Edited by G Silini North Holland Publ Co Amsterdam 1967

TAHMISIAN TH N Cytological effects *In* Mechanisms in radiobiology Vol I Edited by M Errera and A Forssberg Academic Press New York 1961

THOMLINSON R H Oxygen therapy biological considerations *In* Modern trends in radio therapy p 52 Edited by T J Deely and C A P Wood Butterworths London 1967

TILL J F and MCCULLOCH E A Early repair processes in marrow-cells irradiated and proliferating in vivo Radiat Res 18 (1963) 96

VAN PUTTEN L M Oxygenation and cell kinetics after irradiation in a transplantable osteosarcoma *In* Effects of radiation on cellular proliferation and differentiation p 493 International Atomic Energy Agency Vienna 1968

— and KALLMAN R F The oxygenation status of tumors during fractionated radiation therapy Lecture at the III Congress of Radiation Research Cortina d Ampezzo 1966 J *nat Cancer Inst 40 (1968)* 441

V BORSTEL B C and MOSER H Differential ultraviolet irradiation of the habrobracon egg nucleus and cytoplasma *In* Progress in radiobiology p 211 Oliver and Boyd London 1956

WENDT E Lebendbeobachtungen an bestrahlten Interphasenkernen *Z Zellforsch 49 (1959)* 677

WIDEROE R High energy electron therapy and the two component theory of radiation Acta radiol Ther Phys Biol 4 (1966) 257

— New conceptions in radiobiology and radiotherapy Radiol clin Biol 36 (1968) 308

— Tumor therapy with high energy ionizing radiation Kerntechnik 11 *(1969) 312*

— A quantitative analysis of treatment schemes with various types of radiation Atomkern energie 14 (1969) 352

— *A discussion of the oxygen effect* based upon the two component theory of radiation Radiol clin Biol 39 (1970) 20

WITHERS H R and ELKIND M M Radiosensitivity and fractionation response of crypt cells of mouse jejunum Radiat Res *38 (1969)* 598

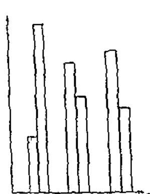


Fig 4

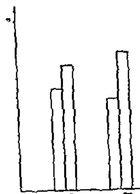


Fig 5

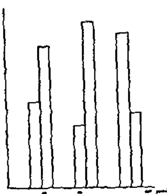


Fig 6

Fig 4 Strong reactions with low linear activities i e with long times in the cases

Fig 5 The maximum dose appears to play no part in the reactions

Fig 6 Some weakening occurs perhaps in those over 70 years

the dose for which the cobalt is responsible (the volume of the target often being different) The doses used in both techniques have been tentatively added Fig 1 indicates that the dose plays no part in the reactions the interval between the cobalt and iridium administrations constitutes the primary factor The cobalt cases were therefore excluded Fig 2 (in which the darkened zones represent the strong reactions) indicates the few reactions when the dose at the hull was under 5 000 rad this eliminates such cases The number of the cases is thus reduced to 91 These were treated by curietherapy only, with doses at the hull up to 6 000 rad

It appeared that lesions of the tongue would produce stronger reactions than in other situations (lips eyelids) where they were treated in smaller volumes As will be explained later the reaction increases with the volume The back-of hand locations demand special consideration (5 strong reactions in 5 cases)

The occurrence of strong reactions increases with the volume of the tumour the proportion ranging from 42 to 62 per cent (Fig 3 a) If however the volume of the area irradiated is also considered the strong reactions rose from 36 to 86 per cent so that the tumour volume in relation to the irradiated volume may be neglected (Fig 3 b)

Fig 4 gives the linear activities employed It might be inferred that the percentage of strong reactions would increase in inverse ratio to the linear activity In fact this activity is closely related to the time of irradiation the dose and location being unchanged Accordingly direct investigation of the influence

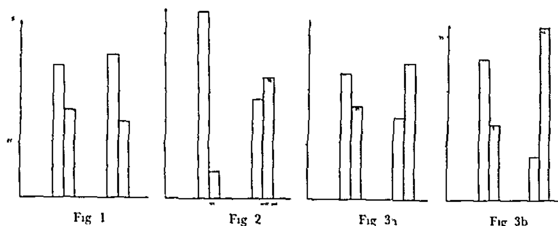


Fig 1 Reactions with cobalt + iridium The dose plays no part in the reactions

Fig 2 Reactions and dose at the hull Few strong reactions with doses under 5 000 rad

Fig 3 a) Strong reactions increase with the tumour volume b) The proportion of strong reactions increases with the irradiated volume in the same cases

limiting the smallest area containing the whole tumour), (5) the location (6) the volume of the malignant lesion, (7) the linear activity, (8) the total activity, (9) the maximum dose, (10) the age of the patient, (11) the ratio of the area of the 50 per cent isodose to the area of the 100 per cent isodose, (12) the basic dose, (13) the irradiated volume, (14) the time of irradiation

Since the aim was to observe the varying biologic effects it was necessary to concentrate upon the most easily recorded biologic sign the reactions of the skin and mucosa These were divided into

Weak reactions No reaction at all, I and II mucitis or epidermitis, unlabelled reactions waning before 45 days

Strong reactions III mucitis or epidermitis, unlabelled reactions lasting more than 45 days, necrosis

It was apparent that necroses would occur in 85 per cent of the total number of cases (11/13) before the third month, so that a period of six months was considered sufficiently long for a case to qualify for investigation They also occurred in 5 per cent of the cobalt associated cases (11/44) compared with only 15 per cent of the curietherapy only cases (13/70), so that the former were excluded

The determination of the influence of the time factor in the local reactions necessitates the elimination of the largest possible number of disturbing factors especially the dose The curietherapeutic doses at the hull range from 3 000 rad to 6 000 rad when cobalt is associated with iridium and it is difficult to assess



Fig 10



Fig 11

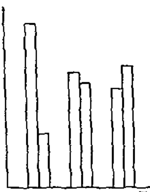


Fig 12

Fig 10 The strong reactions occur more frequently as the time of irradiation increases

Fig 11 The number of patients is too small for the reactions to be affected significantly by the time (volume 20 ml)

Fig 12 The percentage of strong reactions in these small volumes seems to increase with the time of irradiation (volume 70 ml)

Large volumes No reaction occurred after a short time but the number of the patients was too small for these results to be significant Strong reactions were evident in the large volumes under irradiation for a long time (*Fig 11*) The influence of the time could be identified with that of the volume in those cases in which the volumes were large

Small volumes Fig 12 confirms the previous results the percentage of strong reactions *in the* small volumes seems to increase with the time of irradiation

Conclusions

The causes of local reactions have been reduced to the volume and time the reactions appear to increase directly with volume and with the time of irradiation A significant statistical analysis would be possible if a number of curietherapists would participate as a working group with common techniques and well defined objects (locations doses and characterization of reactions)

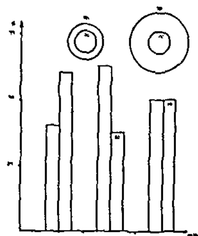


Fig 7

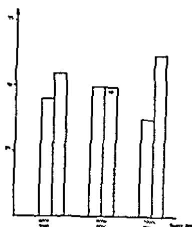


Fig 8

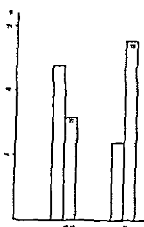


Fig 9

Fig 7 The isodose area 50 %/isodose area 100 % played no significant part in the reactions
Fig 8 The basic dose factor appears to be insignificant
Fig 9 The percentage of strong reactions increases with the volume

of the linear activity has been neglected, since this is equivalent to an indirect investigation of the influence of the time

Nearly all the irradiations were less than 40 mCi The total activity is more important in radiation protection than radiation biology

The maximum dose in only 52 patients could be considered individually Fig 5 indicates that, as was presumed previously, the maximum dose appears to play no part The influence of age is doubtful though a weakening of the reactions may be evident after 70 This factor may be ignored (Fig 6)

It had been assumed that the volume limited by the hull is perhaps not a characteristic parameter and that the peripheral cylinder, weakly irradiated (100 to 50 per cent — 6 000 rad to 3 000 rad) could play a significant part This was contradicted by Fig 7

The basic dose in interstitial curietherapy is at the middle of the broadest lateral canal (PIERQUIN et coll 1969) For a moulded in apparatus the dose lies at the point of contact nearest to the middle of the broadest lateral canal of the apparatus This factor is insignificant (Fig 8) The irradiated volume seems to be an important factor, since the percentage of the strong reaction increases with volume (Fig 9) Fig 10 indicates that strong reactions occur more frequently as the time of irradiation increases Such a result, which contradicts a *former hypothesis was confirmed in all the work* As it was thought that the volume could be a determining factor, an attempt was made to eliminate this factor

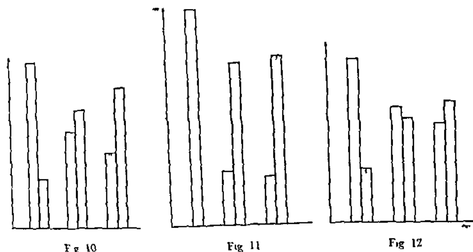


Fig 10 The strong reactions occur more frequently as the time of irradiation increases

Fig 11 The number of patients is too small for the reactions to be affected significantly by the time (volume 20 ml)

Fig 12 The percentage of strong reactions in these small volumes seems to increase with the time of irradiation (volume 20 ml)

Large volumes No reaction occurred after a short time but the number of the patients was too small for these results to be significant Strong reactions were evident in the large volumes under irradiation for a long time (Fig 11) The influence of the time could be identified with that of the volume in those cases in which the volumes were large

Small volumes Fig 12 confirms the previous results the percentage of strong reactions in the small volumes seems to increase with the time of irradiation

Conclusions

The causes of local reactions have been reduced to the volume and time the reactions appear to increase directly with volume and with the time of irradiation A significant statistical analysis would be possible if a number of curietherapists would participate as a working group with common techniques and well defined objects (locations doses and characterization of reactions)

SUMMARY

A series of 151 patients treated by 192 iridium is reviewed The reactions of the skin and mucosa appeared to increase with the volume as well as with the time of irradiation

ZUSAMMENFASSUNG

Eine Übersicht von 151 Fallen die mit 192 Iridium behandelt worden waren wird abgegeben Die Reaktion von Haut und Schleimhaut verstarkt sich entsprechend dem Volumen und der Dauer der Bestrahlung

RÉSUMÉ

Les auteurs ont reexamine une serie de 151 malades traites par l iridium 192 Les reactions de la peau et des muqueuses paraissent augmenter avec le volume irradie et avec la durée d irradiation

REFERENCES

ELLIS F Fractionation in radiotherapy *In* Modern trends in radiotherapy Vol 1 Chapter 2 Edited by T J Deeley and C A P Wood Butterworths London 1967

— The relationship of biological effect to dose time fractionation factors in radiotherapy *In* Current topics in radiation research Vol 4 Chapter 7 Edited by M Ebert and A Howard *North Holland Publishing Co Amsterdam 1968*

FOWLER J F Radiation biology as applied to radiotherapy *In* Current topics in radiation research Chapter 7 Edited by M Ebert and A Howard North Holland Publishing Co Amsterdam 1966

— Effect of fractionated irradiation on the skin of pigs and other animals and on tumours *in rads* Proc *Symp on dose ratein mammalian radiation biology* Oak Ridge UT AEC Paper 21—1—conf 680—410 (1968)

— THOMLINSON R H and HOWES A E Time dose relationship in radiotherapy Europ J Cancer 207 (1970)

— MORGAN R L SILVESTER J A et coll Experiments with fractionated X ray treatment of the skin of pigs I fractionation up to 28 days *Brit J Radiol 36 (1963) 188*

PIERQUIN B DUTREIX A WAMBERSIE A et coll La dosimétrie prévisionnelle en endocurie therapie J Radiol Electrol 50 (1969) 377

REGAUD CL et NOGIER TH Les effets produits sur la peau par les hautes doses de rayons X sélectionnés par filtration a travers 3 et 4 mm d Al Arch Élect méd 22 (1913) 49 et 97

FROM THE RADIATION PHYSICS DEPARTMENT (DIRECTOR PROF G HETTINGER),
UNIVERSITY OF UMEA SWEDEN

DOSIMETRIC MEASUREMENTS AT THE NORDIC MEDICAL ACCELERATORS

II Absorbed dose measurements

by

H SVENSSON

The measurements performed in order to define the beams emitted from betatrons and linear accelerators in 11 Nordic laboratories were summarized in a previous paper (SVENSSON & HETTINGER 1971) The present paper describes measurements of absorbed dose carried out with the same accelerators These investigations were performed during a 3 month tour to the accelerator centres in 1968

The aim of these investigations was to determine differences in the basic dosimetry of the different laboratories to investigate the possibility of establishing uniform dosimetry employing simple measuring equipment and to account for and compare depth dose curves obtained from the uniformly measured and defined radiation beams The discrepancies in absorbed dose calibration factors of thimble ionization chambers and in depth dose curves arising from differences in the constructional details of the accelerators are also discussed

Submitted for publication 13 July 1970

Experiments

Phantom material and size

Various materials have been used for phantoms in different laboratories, accordingly, phantoms of wax, polystyrene, perspex, pressed wood and water were used in measuring the isodose curves published in the IAEA catalogue (WEBSTER & TSIEN 1965). Several of these materials were of different densities and compositions in various laboratories.

In the present study the absorbed dose was determined in water. When measuring technique required use of another phantom material — polystyrene for film dosimetry — factors were determined which allowed correction to the conditions pertaining to a water phantom. The reasons underlying this procedure were: (1) that absorption and scattering properties of muscle tissue and water are very similar (RASSOW 1969), (2) that comparisons between various laboratories are simplified by the constant consistency of water, and (3) that Hospital Physicists' Association, HPA, (1969), and International Commission on Radiation Units and Measurements, ICRU, Report No. 14 (1969) proposed that the absorbed dose of high energy photon radiation be determined in water.

A 30 × 30 × 30 cm water phantom was used in measuring the absorbed dose in water with $FeSO_4$ dosimeters or thimble chambers. The wall facing the beam was made of 0.6 cm thick clear polystyrene, the others were made of perspex.

Dosimeter system

Ferrous sulfate dosimeters. A detailed description of the ferrous sulfate dosimeter technique used in this investigation has been given by PETTERSSON & HETTINGER (1967).

With an irradiation temperature of 25.0° C G values (0.4 mole/l H_2SO_4) of 0.1556 ± 0.0012 eV^{-1} and 0.1557 ± 0.0014 eV^{-1} (standard errors) were employed for electron and ^{60}Co γ radiation respectively (PETTERSSON 1967). For roentgen rays 5 to 10 MV and exceeding 11 MV, the G values were considered to be 0.156 eV^{-1} and 0.157 eV^{-1} respectively (ICRU, Report No. 14, 1969).

Polystyrene or polyethylene irradiation cells were used. The effect on the dosimeter solution by storing in these plastic cells has been reported by SVENSSON et coll. (1967).

With photon radiation the absorbed dose in the dosimeter solution is mainly contributed from electrons originating in the water and in the ferrous sulfate solution as the dosimeter walls and the cell holder of polystyrene are made of thin materials. The mass energy absorption coefficient was considered to be the same for water and for the dosimeter solution when photon radiations with

effective energies between those of ^{60}Co γ radiation and 43 MV roentgen rays were used (SHALEK & SMITH 1969) With both photon and electron radiation the ratio between the absorbed dose in water (D_w) and that in the dosimeter solution (D_d) is therefore equal to the ratio between the mass stopping power of the water and solution, i e

$$\frac{D_w}{D_d} \approx 1\ 004 \qquad (1)$$

Thimble chambers A Baldwin Farmer roentgen ray dosimeter (0 6 cm^3 ionization chamber) and a Siemens Sondenfingerhutkammer connected to an automatic compensating Townsend circuit (WICKMAN to be published) was used The chambers were calibrated with ^{60}Co γ radiation at the Swedish National Institute of Radiation Protection (in 1964 1966 and 1967) and with 2 MV radiation at National Physics Laboratory (NPL) England (in 1968) The calibration factor in R/scale division from the former laboratory was 1 5 % lower than that from NPL The lower calibration factor was used in the present investigation to allow comparisons with earlier publications

Instrument control The instruments were transported by car between the accelerator laboratories in Sweden Finland Norway and Denmark The thimble chambers were checked against each other in each laboratory with a ^{60}Co γ beam and against a commercial (Baldwin Farmer) ^{90}Sr reference source The ionization chamber controls showed a relative standard deviation of 0 2 % during the journey The $FeSO_4$ dosimeters were checked against the thimble chambers with ^{60}Co γ beams and gave a standard deviation of 0 3 %

Measurements of depth dose and depth ionization curves

Depth dose curve The absorbed dose was measured along the central beam in the water phantom with $FeSO_4$ dosimeters The dosimeter cells were placed in a row in a polystyrene holder inside the water phantom Corrections were made taking into account the disturbance of the fluence in the water by the $FeSO_4$ dosimeters and the cell holder The correction factors were determined with an ionization chamber which was irradiated in the water phantom when the $FeSO_4$ dosimeters were and were not present These corrections depended upon the radiation quality and measuring depth and were maximally 1 5 %

Depth ionization curves HETTINGER et coll (1967 a) showed that relative depth ionization curves measured with different commercial thimble ionization chambers agreed for both photon and electron radiation provided that the effective measuring point of the chamber was situated 3/4 r in front of the

centre of the chamber, r being the radius of the chamber cavity The depths of the thimble ionization chamber were set to within 0 2 mm with an automatic device

Absorbed dose calibration of the thimble chambers

Definitions For electron radiation SVENSSON & PETTERSSON (1967) and for roentgen rays HETTINGER et coll (1967 b) defined an absorbed dose calibration factor for thimble ionization chambers, k (rad R^{-1}), which converted the instrument reading to the absorbed dose in water at the effective measuring point through,

$$D_w = k_{^{60}Co} \cdot M \cdot k \text{ or } k = \frac{D_w}{k_{^{60}Co} \cdot M} \qquad (2)$$

where,

D_w is the absorbed dose in water at the position of the measurement point of the chamber when the chamber is replaced by water and an identical irradiation given, rad

$k_{^{60}Co}$ is the ^{60}Co exposure calibration factor of the chamber at a specified temperature and pressure of the air determined in free air at SSD 100 cm and field size 10×10 cm when a 4 mm thick build up cap of perspex is used, R/div

M is the instrument meter reading corrected for general recombination and corrected to air of the same temperature and pressure, div

The definition of the k factors differs from that of the C_λ values defined by HPA (1969) in the respect that an effective measuring point was used, defined above, instead of the centre of the thimble ionization chamber In addition, the C_λ values are defined only for special depths and chamber dimensions

Measurements of absorbed dose calibration factors

A depth dose curve measured with $FeSO_4$ dosimeters and a depth ionization curve measured with a thimble chamber at 32 MV roentgen rays are shown in Fig 1 Similar measurements of depth dose and depth ionization curves were also performed with electron radiation The ratio between the curves at a given depth is according to the definition, equal to the chamber s absorbed dose calibration factor, k at this depth Corrections for the inhomogeneity of the beam were applied since the ionization chambers and the $FeSO_4$ dosimeters have different dimensions orthogonal to the central ray These corrections were determined with photographic films in a polystyrene phantom (SVENSSON & HETTINGER 1971)

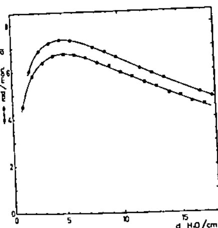


Fig 1

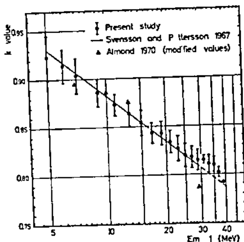


Fig 2

Fig 1 Depth dose curve measured with $FeSO_4$ dosimeters and depth ionization curve measured with thimble ionization chambers 32 MV roentgen rays A water phantom was used The ratio between the curves at a given depth was defined as the absorbed dose calibration factor of the thimble ionization chamber k

Fig 2 Mean values of absorbed dose calibration factors k and their standard deviations obtained from the results of some 20 experiments with different betatrons electron energies (E) field sizes and collimating systems E_m is the mean energy of primary electrons at different phantom depths estimated from eq 3 Comparisons are made with the results from SVENSSON & PETTERSSON (1967) and from modified values of ALMOND (1970)

Results and Discussion

Absorbed dose calibration factors for thimble ionization chambers

Photon radiation k factors were measured with 10 ^{60}Co machines Mean values at different phantom depths are given in Table 1 The purpose of these measurements was to check the instruments the standard deviation of the factors measured at the various machines was 0 3 % The purpose was also to control the absolute dosimetry as this is well established with ^{60}Co γ beams ICRU Report No 14 (1969) thus gives an over all uncertainty of 2 3 % when a calibrated exposure meter is used in water at 5 cm depth for the determination of absorbed dose for ^{60} Co gamma rays The corresponding over all uncertainty with $FeSO_4$ is given to 1 5 % The k factor determined at 5 cm depth ($k = 0\,979$) was converted into (C_λ) defined by HPA (1969) and ICRU Report No 14 (1969) The conversion meant that the centre of the thimble chamber was taken as the measurement point instead of the effective measurement point used with k factors

centre of the chamber, r being the radius of the chamber cavity. The depths of the thimble ionization chamber were set to within 0.2 mm with an automatic device.

Absorbed dose calibration of the thimble chambers

Definitions. For electron radiation SVENSSON & PETTERSSON (1967) and for roentgen rays HETTINGER et coll. (1967 b) defined an absorbed dose calibration factor for thimble ionization chambers, k (rad R^{-1}), which converted the instrument reading to the absorbed dose in water at the effective measuring point through,

$$D_w = k_{^{60}Co} \cdot M \cdot k \text{ or } k = \frac{D_w}{k_{^{60}Co} \cdot M} \quad (2)$$

where,

D_w is the absorbed dose in water at the position of the measurement point of the chamber when the chamber is replaced by water and an identical irradiation given, rad.

$k_{^{60}Co}$ is the ^{60}Co exposure calibration factor of the chamber at a specified temperature and pressure of the air determined in free air at SSD 100 cm and field size 10×10 cm when a 4 mm thick build up cap of perspex is used, R/div.

M is the instrument meter reading corrected for general recombination and corrected to air of the same temperature and pressure, div.

The definition of the k factors differs from that of the C_λ values defined by HPA (1969) in the respect that an effective measuring point was used, defined above, instead of the centre of the thimble ionization chamber. In addition, the C_λ values are defined only for special depths and chamber dimensions.

Measurements of absorbed dose calibration factors

A depth dose curve measured with $FeSO_4$ dosimeters and a depth ionization curve measured with a thimble chamber at 32 MV roentgen rays are shown in Fig. 1. Similar measurements of depth dose and depth ionization curves were also performed with electron radiation. The ratio between the curves at a given depth is according to the definition, equal to the chamber's absorbed dose calibration factor, k, at this depth. Corrections for the inhomogeneity of the beam were applied since the ionization chambers and the $FeSO_4$ dosimeters have different dimensions orthogonal to the central ray. These corrections were determined with photographic films in a polystyrene phantom (SVENSSON & HETTINGER 1971).

Table 2

Comparisons between k and C_λ values determined in the present study and the C_λ values given by HPA 1969. The factors refer to the Stockholm ^{60}Co γ ray exposure calibrations (in 1964, 1966 and 1967). They are 1.5 % lower when the NPL 2 MV exposure calibration (in 1968) is applied.

Radiation	Author's result		Recommended values HPA (1969)
	k	C_λ	C_λ
Co γ-beam	0.93	0.96	0.95
5 MV	0.95	0.94	0.94
6 MV	0.94	0.93	0.94
25 MV			0.90
27.5 MV	0.90	0.89	
30 MV			0.89
32 MV	0.90	0.89	
35 MV			0.88
43 MV	0.89	0.89	

ficiently to produce a uniform field of about 8 cm in diameter at a distance of 1 meter. In one series of experiments the k factors were also measured with 32 MV for non filtered (γ_1) roentgen rays. The k factors (Table 1) were somewhat higher for non filtered than for filtered radiation for depths between 4 and 8 cm. This may imply a greater degree of beam contamination by electrons with non filtered than with filtered radiation.

With the other accelerators investigated, filters were used which gave a flattened field larger than 14 cm in diameter (SSD ≈ 100 cm).

The k values were almost independent of phantom depth for ^{60}Co γ beam, 5 and 6 MV radiation; they were, however, about 1 % higher with 27 to 43 MV radiation at 5 to 6 cm depth than at other depths studied. If the centre of the chamber had been defined as the measuring point, the differences between the ratio absorbed dose to ionization at 5 to 6 cm depth and at greater depths would have further increased. The difference would also have been dependent upon the size of the chamber. These facts were some of the reasons for defining the k values different from C_λ.

Table 2 summarizes the k factors for depths at which C_λ values are defined by HPA (1969). C_λ values have been calculated from the k values and compared with those recommended by HPA. Maximum differences of about 1 % were found if the Stockholm exposure calibration was used. With the NPL calibration the experimental C_λ values were 1 to 2.5 % lower than the recommended ones for roentgen ray beams between 5 and 43 MV. The low values are, however, in

Table 1

Absorbed dose calibration factors of Siemens Sondenfingerhut and Baldwin Farmer (0.6 cm³) chambers for photon radiations The factors refer to the Stockholm ^{60}Co γ ray exposure calibrations (in 1964 1966 and 1967) They are 1.5% lower with the NPL 2 MV exposure calibration (in 1968)

Energy	^{60}Co	5 MV	6 MV	27 MV	32 MV without flattening filter	32 MV with flattening filter	43 MV
Number of investigated units	10	1	2	1	1	4	1
G value (eV⁻¹)	0.1557	0.156	0.156	0.157	0.157	0.157	0.157
Depth d/cm							
3	0.98	0.95	0.94	0.89	0.90	0.90	0.88
5	0.98	0.95	0.94	0.91	0.92	0.91	0.90
7	0.98	0.94	0.94	0.90	0.91	0.91	0.89
9	0.98	0.94	0.94	0.90	0.90	0.90	0.89
11	0.98	0.94	0.94	0.90	0.90	0.90	0.89
13	0.97	0.94	0.94	0.90	0.90	0.90	0.89
15	0.97	0.94	0.93	0.88	0.89	0.90	0.88

The present investigation gave $(C_\lambda)_c = 0.963$ with the exposure calibration from Stockholm, and $(C_\lambda)_c = 0.949$ with the calibration from NPL, thus in good agreement with the value 0.95 recommended by HPA (1969)

Table 1 also summarizes λ factors as a function of measuring depth for roentgen rays between 5 and 43 MV The beams were not as well flattened as by ^{60}Co gamma rays and systematic errors might be introduced when the corrections were applied for the different dimensions of the $FeSO_4$ dosimeters and the thimble ionization chambers The over all uncertainty in the measurement technique with the accelerators (not including errors in the exposure calibration factors, extinction coefficient, and G value) was estimated to be within ± 1 % (Statement of accuracy according to ICRU Report No 12, 1968)

Within the relative accuracy of about ± 1 % the same λ factors were measured at 32 MV (γ_2) with the four BBC betatrons investigated Also with the two Varian 6 MV linear accelerators the same λ factors were obtained within ± 1 %

Three different beam flatteners can be used with BBC betatrons, denoted γ_2, γ_3 and γ_4 The smallest flattener, γ_2, was chosen above in order to obtain as high an absorbed dose rate as possible for irradiating the $FeSO_4$ dosimeters This flattener (γ_2) had a thickness of lead necessary to flatten the isodose curves suf

Table 3

Comparisons between k/A measured with Siemens Sondenfingerhut or with Baldwin Farmer chambers and calculated D_w/J (

Radiation		k/A	D_w/J tr		
E_0/MeV	d cm H_2O	Present investigation	HARDER (1965)	BERGER & SELTZER (1969)	KESSARIS (to be published)
10	1.0	0.89	0.89	0.90	0.89
	2.0	0.90	0.90	0.91	0.90
15	2.0	0.87	0.88		0.87
20	2.0	0.85	0.86	0.86	0.85
25	2.0	0.83	0.84		
30	2.0	0.82	0.83	0.83	
35	2.0	0.82	0.82		
40	2.0	0.81	0.81	0.81	
	5.0	0.83	0.83	0.83	0.82

by energy range analysis using a relation for the present purpose not significantly different from the equation used by SVENSSON & HETTINGER (1971). The absorbed dose in water was measured with $FeSO_4$ dosimeters with the same G values as applied in the present investigation. ALMOND (1970) obtained on an average slightly higher absorbed dose calibration factors than SVENSSON & PETTERSSON (1967) (eq. 4). Measurements made with one BBC-betatron in the present study with 13 and 31 MeV radiation showed, however, that ionization in a Baldwin Farmer chamber was somewhat higher, approximately 1.6 %, when irradiated at a position corresponding to the absorbed dose maximum in water, than when irradiated at an equivalent position in a polystyrene phantom. ALMOND's results differ from the present values by a maximum of about ± 1.5 % after applying this correction (Fig. 2).

SVENSSON et coll. (to be published) showed that k factors for 6 different types of commercial thimble chambers of volumes ranging from 0.1 to 3 cm³ agreed within ± 2 %. The measurements were carried out at the depth of the peak absorbed dose at energies ($\bar{E}_m$) between 5.5 and 26.4 MeV. The authors explained the differences between the k factors for the different chambers from stem leakage effect, scattering from the stem to the chamber cavity and from the fact that the electron fluence is larger in the chamber's gas cavity than it would be when the gas is replaced with water. This latter effect is due to the different scattering properties of the gas and water (HARDER 1968). These effects were small, jointly less than 1 % for Siemens Sondenfingerhut and Baldwin Farmer chambers. Both these chambers were used in the measurements in the Nordic

good agreement with the experimental C_λ from BEWLY (1963) at 8 and 14 MV and ALMOND (1968) at 18 5 and 22 MV

Electron radiation SVENSSON & PETTERSSON (1967) showed that, absorbed dose calibration factors measured with Siemens Sondenfingerhut and Philips intracavity chambers depended only upon the average energy, E_m of the electrons at the measuring point E_m was determined from the relation (HARDER 1965)

$$E_m = E_o \ (1 - d/R_p) \qquad (3)$$

where

E_o is the electron energy at the phantom surface, MeV,
d is the depth of the effective measuring point of the chamber, cm,
R_p is the extrapolated practical range, cm

Other parameters of the beam, e g field size (larger than Ø 5 cm), SSD (between 110 and 130 cm), and construction of the collimating system had no significant influence on the factors Absorbed dose calibration factors, k, for energies, E_m between 5 and 30 MeV, were determined by the authors to,

$$k = C_1 - C_2 \log_{10} (C_3 \ E_m + 1) \qquad (4)$$

where

$C_1 = 1\ 045$ rad/R
$C_2 = 0\ 161$ rad/R
$C_3 = 1$ MeV^{-1}

Measurements were carried out with 10 betatrons to determine if the absorbed dose calibration obtained by SVENSSON & PETTERSSON (1967) with one betatron could be employed by other laboratories E_o was determined by range analysis in a uniform way (SVENSSON & HETTINGER 1971) The energy at the phantom surface, E_o was varied from 13 to 42 MeV For each E_o central axis depth dose and depth ionization curves were measured and the k factors at different depths, d in eq 3, were calculated Geometrical field sizes equal to or larger than 6 cm were used

The standard deviation of the k factors for a fixed energy, E_m was about 1 5 % No systematic dependency on the betatron, incident energy and field size used could be found Comparisons between the results from all the betatrons and from SVENSSON & PETTERSSON (1967) are shown in Fig 2 The agreement was very good

ALMOND (1970) measured absorbed dose calibration factors in a SCRAD type polystyrene phantom for Baldwin Farmer and Shonka Wykoff chambers The centres of the chambers were taken as measuring points The position of the effective measuring point was not critical since measurements were made at a depth corresponding roughly to the absorbed dose maximum E_o was determined

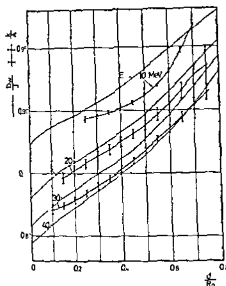


Fig 3

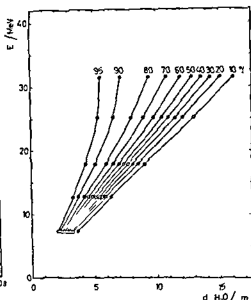


Fig 4

Fig 3 Compari ons of k/A measured with a Siemens Sondenfingerhutkammer and theoretical D_w/J from BERGER & SELTZER (1969) The depths along the central ray are given as d/R_p (depth d/cm H_2O and extrapolated practical range R_p/cm H_2O) The k/A factors were det rmined from several independent series of experiments (4 10 and 8 with 10 20 and 30 MeV respecti ely) and with different betatrons The field s zes are $\geq 8 \times 10$ cm The standard deviations of the mean values a e given Two series of k/A measurements were also mad with 40 MeV These factors were scattered around the D_w/J curve and agreed within 1 with this for d/Rp between 0 1 and 0 75 (The experimental $k/$ 1 values with 40 MeV are not hown in the figure)

Fig 4 Depth dose data for a given field size (14×14 cm) versus depth for fixed relative depth doses BBC 35 MeV betat on at laboratory No 2 Relative depth dose curves for given energies were extracted f om such series of results gi en in Tables 6 and 7

KESSARIS (to be published) (Table 3) In the table D_w/J values corresponding approximately to the depth of the peak absorbed dose are given It can be een that the k/A and D_w/J_a values differ by a maximum of 2 % Values of k/A were al o compared with D_w/J for various E_o and d (Fig 3) These D_w/J_a values were taken from BERGER & SELTZER (1969) who have performed more complete theoretical calculations of electron spectra for various E and d than other investigators The comparisons showed that the maximum difference between theory and experiment is about 2 % with energies E between 10 and 40 MeV and depths between 1 5 cm and about 0 8 R_p The maximum difference had been about 1 % if the comparisons had been carried out between k/A for an ideal thimble ionization chamber and D_w/J_a (see above) Again as with roentgen

Table 4

The discrepancies in the local calibrations of absorbed dose. The author's results were chosen as a reference. The table covers approximately 120 comparisons with different combination of energy and field size. The extreme variations at the various laboratories are given. The percentage difference in rad/scale division or rad/minute between visited laboratory and reference are shown

Laboratory number	γ rays ^{60}Co	Rtg rays 16—40 MV		e⁻ 10—15 MeV		e⁻ 30—35 MeV	
1	−1.5	+[illegible]		+6			
2	−1.5	0		−6	−3	−4	−2
3	0	+2		+14	+18	+17	+19
4	+1.7	−13	−3	−2	+1	−1	+1
5		−5	−1	−8	+1	−7	−5
6	−1.2						
7	+0.1	−2		+18			
8		−5	+10	−1	+1	−5	+2
9	−0.5	+5		−4	+6		
10		0		0		0	
11	0	0		0		0	

countries. With respect to these effects, the results in Fig. 2 are therefore valid within approximately 1 % for an ideal thimble ionization chamber. The differences between the factors were largest at low energies where the k factors for the chambers used, are lower than for an ideal one.

A comparison between experimental absorbed dose calibration factors and theoretically determined D_w/J_{air} values were made. The following assumptions were employed. If A is a correction for photon attenuation for ^{60}Co γ rays in build up material used at exposure calibration then $A \cdot k_{^{60}Co} \cdot M$ yields approximately the ionization calibration in e.s.u. per $1.293 \cdot 10^{-3}$ g air, not only for ^{60}Co γ-rays but also for high energy electrons (SVENSSON & PETTERSSON 1967). The whole attenuation of the wall and build up cap, together about 0.5 g/cm² was not included in the correction A as most of the electrons which give ionization in the cavity origin upstreams in the beam (BURLIN 1968). The correction factor A was estimated to 0.985.

From eq. 2

$$\frac{k}{A} = \frac{D_w}{A \cdot k_{^{60}Co} \cdot M} \approx \frac{D_w}{J_{air}}$$

Value of k/A for a Siemens Sondenfingerhutkammer were compared with the theoretical D_w/J_{air} values of HARDER (1965), BERGER & SELTZER (1969), and

Table 5 *(cont)*

BBC 35 MeV betatrons			
32 MV			
4×4 (/1)*	4×4 (y4)*	8×8 (?)*	16×16 (/4)*
7	7	6	7
86 4 (0 6)	88 7 (1 4)	86 0 (0 5)	92 6 (0 6)
95 4 (0 4)	96 6 (0 4)	95 0 (0 4)	98 2 (0 4)
99 2 (0 2)	99 7 (0 2)	98 8 (0 5)	100 0 (0 2)
100 0 (0 2)	100 0 (0 1)	100 0 (0 1)	99 4 (0 3)
99 2 (0 3)	98 6 (0 3)	99 3 (0 3)	97 3 (0 7)
97 1 (0 5)	96 1 (0 4)	97 6 (0 6)	94 5 (0 9)
94 2 (0 6)	93 1 (0 5)	95 2 (0 6)	91 4 (0 9)
91 0 (0 5)	89 7 (0 6)	92 2 (0 6)	88 3 (0 9)
87 5 (0)	86 4 (0 7)	89 1 (0 4)	85 1 (0 8)
81 0 (0 5)	79 9 (0 8)	87 7 (0 4)	79 2 (0 8)
74 9 (0 6)	73 8 (0 8)	76 7 (0 5)	73 6 (0 9)
69 (0 7)	68 1 (0 8)	71 0 (0 4)	68 5 (1 1)
63 9 (0 7	62 9 (0 8)	65 8 (0 3)	63 9 (1 2)
59 1 (0 7)	58 2 (0 8)	61 1 (0 3)	59 4 (1 2)
54 7 (0 7)	53 9 (0 7)	56 6 (0 3)	55 3 (1 2)
50 6 (0 7)	49 9 (0 8)	52 5 (0 4)	51 6 (1 2)
46 8 (0 7)	46 3 (0 8)	48 8 (0 3)	48 1 (1 3)

tion of absorbed dose along the central ray (between the depth 1 5 cm to about 0 8 R_p) with different betatrons in the energy range (E) 10 to 40 MeV, provided that electron energies (E_o) are determined by methods described by SVENSSON & HETTINGER (1971) Absorbed dose calibration factors from Table 3 may be used for determining absorbed dose at the depth of peak absorbed dose along the central beam, the factors from Fig 2 (eq 4) and Fig 3 may be used when the absorbed dose in the central beam is required at other depths

Intercomparisons of absorbed dose calibrations

The dosimetric technique with thimble ionization chambers described above was used by the author The discrepancies between the absorbed dose calibrations

Table 5

Mean percentage depth dose data at a given depth for high energy photons with separate accelerators and within parentheses standard deviations of the percentage SSD was 100 cm

Type of accelerator	AEI 5 MV lin acc	Varian 6 MV linear accelerator			Siemens 42 MeV betatron	
Energy	5 MV	6 MV			27.5 MV	43.5 MV
Field size (cm)	10 × 10	6 × 6	10 × 10	20 × 20	15 × 15	15 × 15
Investigated accelerators	1	1	2	1	1	1
Depth (cm)						
1.3	100.0	100.0	100.0	100.0		
2	97.6	99.2	99.0	98.7	97.7	92.8
3	92.3	94.9	95.0	95.1	100.0	98.4
4	87.7	90.2	90.7	91.2	98.5	100.0
5	83.5	85.7	86.4	87.5	95.9	99.3
6	79.5	81.2	82.4	83.8	92.9	97.7
7	75.4	76.9	78.5	80.3	89.7	95.5
8	71.4	72.7	74.6	76.8	86.6	93.1
9	67.6	68.7	71.0	73.6	83.5	90.3
10	63.8	64.8	67.4	70.3	80.6	87.4
12	57.0	57.8	60.7	64.2	74.8	81.4
14	50.8	51.6	54.5	58.3	69.3	76.0
16	45.3	46.0	48.9	53.2	64.1	70.7
18	40.5	41.1	43.9	48.3	59.3	65.7
20	36.2	36.7	39.5	43.9	55.2	61.0
22	32.4	32.8	35.5	40.0	51.4	56.7
24	29.0	29.3	31.8	36.3		52.8
26						

* Beam flattener

rays, the k factors had been lower than the theoretical ones if the NPL exposure calibration had been used instead of the one from Stockholm

G values have been assumed to be independent of phantom depth and electron energy in the present investigation This assumption may not be quite valid In this respect, PINKERTON (1969) observed a slight elevation ($\approx 2\%$) of the G value at the end of the depth dose curve at 18 % depth dose level The elevation, however, was not considered significant ALMOND (1967) found some evidence for a slight variation of the G value with electron energy over the range of 13 to 18 MeV

The present investigation showed that commercial ionization chambers, calibrated with a ^{60}Co γ beam, could be used within about 2 % for uniform calibra

Table 6

Mean depth dose data (in cm) for a given percentage depth dose for high energy electrons with BBC 35 MeV betatrons and within parentheses the standard deviations for the different BBC betatrons

Energy (MeV)	Field size (cm)	Investigated BBC betatrons	Percentage depth dose* 95	90	80	70	60	50	40	30	20	10
6	~12×12	1	1 7	1 8	1 9	2 1	2 2	2 3	2 4	2 5	2 6	3 0
10	ø 5	1	2 2	2 5	3 0	3 3	3 6	3 8	4 1	4 3	4 5	5 0
	8×10	2	2 5	2 7	3 1	3 4	3 6	3 9	4 1	4 3	4 5	4 9
	~12×12	6	2 6	2 8	3 2	3 4	3 6	3 9	4 1	4 3	4 5	4 9
			(0 1)	(0 1)	(0 1)	(0 1)	(0 1)	(0 1)	(0 1)	(0 1)	(0 0)	(0 1)
15	ø 4	3	2 5	2 9	3 6	4 2	4 6	5 1	5 6	6 1	6 6	7 3
			(0 0)	(0 1)	(0 1)	(0 1)	(0 1)	(0 1)	(0 1)	(0 0)	(0 1)	(0 2)
	ø 6	1	3 3	3 8	4 5	4 9	5 3	5 7	6 0	6 4	6 7	7 2
	ø 8	6	3 5	4 0	4 7	5 2	5 6	5 9	6 2	6 6	6 9	7 5
			(0 2)	(0 1)	(0 2)	(0 2)	(0 2)	(0 2)	(0 2)	(0 2)	(0 3)	(0 3)
	4×8	2	2 9	3 5	4 2	4 8	5 1	5 7	6 1	6 4	6 9	7 4
	8×10	8	3 7	4 3	4 9	5 3	5 7	6 1	6 4	6 7	7 0	7 5
			(0 2)	(0 1)	(0 1)	(0 1)	(0 1)	(0 1)	(0 0)	(0 1)	(0 1)	(0 1)
	12×12	8	3 8	4 3	5 0	5 4	5 7	6 0	6 3	6 6	7 0	7 4
			(0 2)	(0 1)	(0 1)	(0 1)	(0 1)	(0 1)	(0 1)	(0 1)	(0 1)	(0 1)
20	ø 4	3	2 8	3 4	4 3	5 0	5 7	6 3	7 0	7 7	8 5	9 6
			(0 1)	(0 1)	(0 1)	(0 0)	(0 1)	(0 1)	(0 1)	(0 1)	(0 2)	(0 4)
	ø 6	1	4 2	4 9	5 9	6 5	7 0	7 6	8 1	8 6	9 1	9 8
	ø 8	6	4 3	5 1	6 2	6 9	7 4	8 0	8 5	9 0	9 5	10 3
			(0 2)	(0 2)	(0 1)	(0 1)	(0 1)	(0 1)	(0 1)	(0 1)	(0 2)	(0 4)
	4×8	2	3 4	4 1	5 2	5 9	6 6	7 3	7 9	8 5	9 2	10 0
	8×10	8	4 6	5 5	6 5	7 1	7 7	8 1	8 6	9 0	9 5	10 2
			(0 2)	(0 2)	(0 1)	(0 1)	(0 1)	(0 1)	(0 1)	(0 1)	(0 1)	(0 2)
	~12×12	8	4 7	5 6	6 6	7 3	7 8	8 2	8 6	9 0	9 5	10 1
			(0 2)	(0 2)	(0 1)	(0 1)	(0 0)	(0 0)	(0 0)	(0 0)	(0 1)	(0 2)

* SSD 110 cm according to the manufactures

determined by the various laboratories and those determined by the author are given in Table 4. The table covers approximately 120 comparisons with different combinations of field size and radiation quality. The intercomparisons were carried out at the peak absorbed dose along the central ray with electrons and roentgen rays. With ^{60}Co γ radiation the reference depth in water was 5 cm.

It can be seen from Table 4 that for ^{60}Co γ radiation a good dosimetric routine provides very good agreement between different laboratories. The difference

Table 6 (cont.)

Energy (MeV)	Field size (cm)	Investigated BBC betatrons	Percentage depth dose* 95	90	80	70	60	50	40	30	20	10
25	⌀ 4	3	3.1	3.8	5.0	5.9	6.7	7.5	8.3	9.3	10.3	11.9
			(0.1)	(0.1)	(0.2)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.2)	(0.3)
	⌀ 6	1	4.7	5.7	6.9	7.8	8.5	9.2	9.9	10.6	11.4	12.4
	⌀ 8	6	4.9	6.1	7.4	8.3	9.1	9.8	10.4	11.1	11.7	12.8
			(0.2)	(0.2)	(0.2)	(0.1)	(0.1)	(0.1)	(0.1)	(0.2)	(0.1)	(0.4)
	4×8	2	3.8	4.8	6.1	7.1	8.0	8.8	9.6	10.4	11.3	12.5
	8×10	8	5.2	6.4	7.8	8.7	9.4	10.1	10.7	11.2	11.9	12.8
			(0.2)	(0.1)	(0.1)	(0.1)	(0.1)	(0.0)	(0.1)	(0.1)	(0.1)	(0.2)
	>12×12	8	5.4	6.6	8.0	8.9	9.7	10.3	10.8	11.3	11.9	12.7
			(0.3)	(0.2)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.3)
30	⌀ 4	3	3.5	4.5	5.8	6.8	7.8	8.7	9.6	10.8	12.1	14.0
			(0.1)	(0.1)	(0.1)	(0.2)	(0.1)	(0.1)	(0.2)	(0.1)	(0.1)	(0.3)
	⌀ 6	1	4.3	5.9	7.6	8.7	9.7	10.5	11.4	12.3	13.2	14.2
	⌀ 8	6	5.4	5.8	8.5	9.6	10.6	11.4	12.3	13.1	13.9	15.1
			(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.0)	(0.2)	(0.1)	(0.3)
	4×8	2	4.5	5.6	7.1	8.2	9.3	10.3	11.3	12.2	13.3	14.8
	8×10	8	5.6	7.1	8.9	10.1	11.0	11.9	12.6	13.4	14.2	15.1
			(0.3)	(0.2)	(0.2)	(0.2)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.2)
	>12×12	8	5.6	7.3	9.2	10.5	11.4	12.2	12.9	13.5	14.3	15.1
			(0.2)	(0.2)	(0.2)	(0.2)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)

between the extreme values of Table 4 was 32 %. Corresponding differences for electron and roentgen radiation were 27 % and 23 % respectively.

The temperature and time dependencies of the monitors of the various accelerators were investigated. The precision of the monitors for both electron and roentgen radiation was better than 3 %. Long time variations of the monitor sensitivity were not possible to check. The discrepancies in Table 4 are however much greater than 3 % and may therefore only partly depend on poor precision of the accelerator monitors. Most of the variations must thus depend on differences in dosimetric methods used by the various laboratories.

Relative depth dose curves

Relative depth dose curves with photon radiation. Table 5 contains relative depth dose curves measured with roentgen rays in this study. Peak photon energies were 5 and 6 MeV according to data supplied by the manufacturers

Table 6

Mean depth dose data (in cm) for a given percentage depth dose for high energy electrons with BBC 35 MeV betatrons and within parentheses the standard deviations for the different BBC betatrons

Energy (MeV)	Field size (cm)	Investigated BBC betatrons	Percentage depth dose*									
			95	90	80	70	60	50	40	30	20	10
6	> 12 × 12	1	1.7	1.8	1.9	2.1	2.2	2.3	2.4	2.5	2.6	3.0
10	[illegible]	1	2.2	2.5	3.0	3.3	3.6	3.8	4.1	4.3	4.5	5.0
	8 × 10	2	2.5	2.7	3.1	3.4	3.6	3.9	4.1	4.3	4.5	4.9
	> 12 × 12	6	2.6	2.8	3.2	3.4	3.6	3.9	4.1	4.3	4.5	4.9
			(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.0)	(0.1)
15	⌀ 4	3	2.5	2.9	3.6	4.2	4.6	5.1	5.6	6.1	6.6	7.3
			(0.0)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.0)	(0.1)	(0.2)
	⌀ 6	1	3.3	3.8	4.5	4.9	5.3	5.7	6.0	6.4	6.7	7.2
	⌀ 8	6	3.5	4.0	4.7	5.2	5.6	5.9	6.2	6.6	6.9	7.5
			(0.2)	(0.1)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.3)	(0.3)
	1 × 8	2	2.9	3.5	4.2	4.8	5.1	5.7	6.1	6.4	6.9	7.4
	8 × 10	8	3.7	4.3	4.9	5.3	5.7	6.1	6.4	6.7	7.0	7.5
			(0.4)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.0)	(0.1)	(0.1)	(0.1)
	12 × 12	8	3.8	4.3	5.0	5.4	5.7	6.0	6.3	6.6	7.0	7.4
			(0.2)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)
20	⌀ 4	3	2.8	3.4	4.3	5.0	5.7	6.3	7.0	7.7	8.5	9.6
			(0.1)	(0.1)	(0.1)	(0.0)	(0.1)	(0.1)	(0.1)	(0.1)	(0.2)	(0.4)
	⌀ 6	1	4.2	4.9	5.9	6.5	7.0	7.6	8.1	8.6	9.1	9.8
	⌀ 8	6	4.3	5.1	6.2	6.9	7.4	8.0	8.5	9.0	9.5	10.3
			(0.2)	(0.2)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.2)	(0.4)
	4 8	2	3.4	4.1	5.2	5.9	6.6	7.3	7.9	8.5	9.2	10.0
	8 × 10	8	4.6	5.5	6.5	7.1	7.7	8.1	8.6	9.0	9.5	10.2
			(0.2)	(0.2)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)	(0.2)
	> 12 × 12	8	4.7	5.6	6.6	7.3	7.8	8.2	8.6	9.0	9.5	10.1
			(0.2)	(0.2)	(0.1)	(0.1)	(0.0)	(0.0)	(0.0)	(0.0)	(0.1)	(0.?)

* SSD 110 cm according to the manufactures

determined by the various laboratories and those determined by the author are given in Table 4 The table covers approximately 120 comparisons with different combinations of field size and radiation quality The intercomparisons were carried out at the peak absorbed dose along the central ray with electrons and roentgen rays With ^{60}Co γ radiation the reference depth in water was 5 cm

It can be seen from Table 4 that for ^{60}Co γ radiation a good dosimetric routine provides very good agreement between different laboratories The difference

Table 7 *(cont.)*

25				35		40			
⊘ 4	⊘ 6	⊘ 8	⊘ 15	⊘ 15	⊘ 15	⊘ 4	⊘ 6	⊘ 8	⊘ 15
β	β_t	β	β*	β	β	β	β	β	β*
3 7	4 5	4 5	4 6	4 6	4 3	3 5	5 0	5 4	5 2
4 6	5 6	5 8	6 2	6 3	5 9	4 9	6 4	6 9	6 8
5 7	6 8	7 3	7 8	8 8	8 2	6 9	8 4	9 1	9 3
6 5	7 8	8 3	8 8	10 6	10 0	8 3	10 1	10 9	11 6
7 3	8 5	9 1	9 7	12 1	11 5	9 6	11 5	12 5	13 5
8 0	9 2	9 7	10 3	13 4	12 8	10 8	12 9	14 0	15 0
8 8	10 0	10 4	10 7	14 4	14 0	12 0	14 2	15 3	16 3
9 6	10 6	11 1	11 3	15 4	15 3	13 4	15 5	16 7	17 5
10 6	11 4	11 7	11 9	16 5	16 5	15 1	17 2	18 2	18 8
11 6	12 2	12 4	12 6	17 9	23 0	17 8	19 4	20 5	20 7

between depth doses at 5 and 15 cm depth was critically dependent upon the peak photon energy at values lower than 10 MV. The beam flattener may also affect the depth dose curve. Table 5 shows that at 32 MV the depth doses at larger depths are less for the larger beam flattener (Ø4) than for the smaller (Ø5). In this energy range this effect can be explained by the increased pair production in the lead flattener which results in a higher percentage attenuation of photons at the high energy end of the spectrum.

Relative depth dose curves with electron radiation. The electron energy at the phantom surface was determined by methods described by SVENSSON & HETTINGER (1971), i.e. by range analysis or by (γ, n) threshold analysis employing corrections for energy losses occurring for instance in tube window and scattering foils. The field size was defined by the geometrical limits of the collimating tubes. The homogeneity index (ratio of the area inside the 80 % isodensity curve at 2 cm depth to the geometrical field area (SVENSSON & HETTINGER 1971)) was on average 0.6 with the BBC betatrons and 0.8 with the Siemens 42 MeV betatron. Depth dose data for a given geometrical field size and accelerator were plotted as energy versus depth for fixed relative depth doses (Fig. 4). Similar curves from different accelerators allowed depth dose data for given energies and field sizes to be extracted (Tables 6 and 7).

Table 7

*Depth dose data for high energy electrons with one Siemens 42 MeV betatron. Depth in cm for a given percentage depth dose. SSD was 100 cm according to the manufacturer ***

Energy (MeV)	6	15				
Field size (cm)	ø 15	ø 4	ø 6	ø 8	ø 15	ø 15
Scattering foil	β_0	β_1	β_1	β_1	β_1*	β_4
Percentage depth dose						
95	1.6	3.3	3.9	4.3	4.4	3.0
90	1.7	3.6	4.4	4.6	4.9	3.6
80	1.8	4.1	5.0	5.1	5.4	4.4
70	2.0	4.7	5.5	5.5	5.7	5.0
60	2.1	5.2	5.8	5.8	6.0	5.5
50	2.2	5.5	6.0	6.1	6.2	5.8
40	2.3	6.0	6.3	6.4	6.5	6.3
30	2.5	6.4	6.6	6.7	6.8	6.7
20	2.6	6.8	6.9	6.9	7.1	7.1
10	2.8	7.3	7.2	7.2	7.4	7.7

* This combination of energy, field size and scattering foil did not give a flattened field.
** The manufacturer recommends SSD 120 cm above 20 MeV.

At higher energies, maximum photon energies were determined with (γ, n) threshold analysis (SVENSSON & HETTINGER 1971). The field size was defined by the geometrical field represented by an illuminated area on the phantom surface.

Relative depth dose curves determined with two Varian 6 MV linear accelerators (Table 5) and those obtained with a Varian 6 MV accelerator by HORSLEY et coll. (1968) agreed within 1 % for corresponding depths. Standard deviations for relative depth dose curves obtained with 6 BBC betatrons at 32 MV were less than 1.5 % for depths up to 15 cm provided that given beam flatteners and field sizes were employed. Relative depth dose data from accelerators of similar construction appear to agree closely.

GREENE (1969) showed that agreement between depth dose curves from different accelerator types was poor. Discrepancies in relative depth dose data of up to 12 % were reported for a depth of 20 cm (35 MV, 10 × 10 cm, FSD 100 cm). The measurements were carried out by the different accelerator laboratories. Differences in the techniques of determining relative depth dose curves may therefore account for some of the deviations. Inaccurately determined maximum photon energies can give rise to discrepancies especially for energies lower than 10 MV. It was thus shown by SVENSSON & HETTINGER (1971), that the ratio

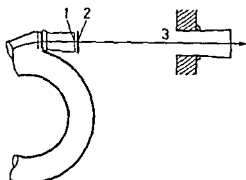
Relative depth dose data from accelerators of similar construction thus appear to agree closely also with electron radiation In contrast depth dose curves from the two betatron types differ significantly

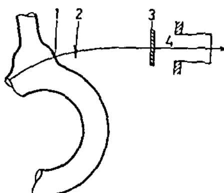
In order to explain these differences the beam geometry was studied (Fig 5) The scattering and energy degradation in the central part of the electron beams from the Siemens betatron occurs almost exclusively in the scattering foils In the BBC betatrons the electrons are scattered and suffer energy losses also in the accelerator window and transmission chambers Since irradiations with the Siemens betatron could be carried out with various thicknesses of the scattering foils it was possible to study the effect of scattering material in the beam upon the depth dose curve Depth dose curves were therefore measured at 15 MeV with 0 1 and 1 mm Pb foil A somewhat higher energy was set on the instrument panel of the betatron when the thicker foil was used to ensure that the energy at the phantom surface should be the same as when the thin foil was used The best depth dose curve was obtained with the thin foil (Fig 6) in agreement with SEMPERT & WIDEROE (1958) and LOEVINGER et coll (1961) The thin foil was however sufficient only to flatten a ϕ 7 cm field at SSD 100 cm and 15 MeV

The difference between the curves obtained with different foils depended upon the greater contamination of the beam by low energy electrons when a thick foil was used An approximate measure of the contamination is provided by the energy degradation in the central part of the beam through radiation and collision processes The mean energy degradation with the thick foil was 4 0 MeV and with the thin foil 0 8 MeV (Fig 5) A depth dose curve measured at 15 MeV with a BBC betatron is also shown in Fig 6 The energy degradation was approximately 2 9 MeV and the depth do e curve better than the one for the flattened field with the Siemens betatron

An increase of the scattering material in the central beam also implies that more electrons are spread out and into the collimating system One part of these electrons may be energy degradated and then cattered back into the central beam and thus deteriorates the depth dose curve The scattering system of a BBC 35 MeV betatron and a proposal for improvement are di cussed in another paper by the author (SVENSSON 1971)

Depth do e curves from BBC betatrons were usually better, compared with Siemens betatrons than could be expected on the grounds of energy losses This may be explained from the fact that the magnetic field outside the tube window of the BBC betatron is sufficient to avert some of the low energy electrons formed in the window thus preventing them from reaching the phantom A similar di version does not occur in the Siemens betatron This may be one of the reasons why the beam is less contaminated by low energy electrons in the BBC betatrons better depth dose curves) than in the Siemens betatrons for 25 MeV and a field





t ing m t i l	$\frac{t}{\rho}$ ρ (15 M V)	$\frac{t}{\rho}$ Δ ρ (t 40 M V)
1) fub wi d w 30 μm C	0 1 (M V)	0 1 (M V)
2) t i g f il		
0 1 mm Pt	(0 4)	(0 8)
0 5	0	(1 9)
β_3 0 5	1 8	3 8
β 1	1 6	7 6
3) Al 1 0 m	0 3	0
Σ E gy d g d t wi h diff t f il		
0 1 mm Pt	(0 8))	(1 3))
β 0 25	1 3	(2 4))
β_3 0 5		4 3
β_4 1 0	4 0	8 1

t i g t i l	$\frac{t}{\rho}$ Δ ρ (t 15 M V)	$\frac{t}{\rho}$ ρ (10 M V)
1) T b wi d ≈ mm gl	1 1 (M V)	1 5 (M V)
2) tt i g f il ≈ 0 mm C	0 9	1
3) T mi i n h mb	0 6	(
4) Al 1 0 m	0 3	0
Σ E gy d g d i	≈ 9	≈1 8

)Tl l ti i f g l g l
id r tl i fl ld

Fig 5 The beam geometry of two makes of betatrons All the scattering materials in the path of the central beam are given

No depths for the 100 % depth doses have been given in the tables The reason lies in the non critical nature of this position The depth dose varies often only by fractions of one per cent over the range 1 to 2 5 cm depth The peak absorbed dose for large field sizes were situated at about 2 cm depth for energies between 10 and 40 MeV

Table 6 contains depth dose curves from 8 BBC betatrons and Table 7 from one Siemens 42 MeV betatron Standard deviations in the depth for a given percentage (e g 95, 90, 80 %) were approximately 1 mm for the BBC betatrons

95 and 90 per cent depth doses with small field sizes (Ø 4 cm in Tables 6 and 7 occurred at smaller depths with the BBC-betatrons than with the Siemens 42 MeV betatron These depth doses occur, however, most often at greater depths with BBC-betatrons for large field sizes Another cause may be that small field sizes are flattened more with Siemens than with BBC betatrons (homogeneity index 0 8 and 0 6 respectively, compare above) and somewhat larger effective field size are thus obtained with the former

SCHULTZ (1969) showed that the depths for 50 % depth dose measured in different laboratories (25 MeV, 10 × 10 cm) differed by up to 1 5 cm POHLIT s (1961) measurements and the present study showed however, that the differences between depth dose curves from different types of betatrons are considerably less A large part of this difference must therefore be ascribed to variations in energy calibration The given energy however is of less importance for usage of the depth dose curves for radiotherapy provided that these curves are accurately known for a given MeV instrument setting

Comparisons between relative depth dose curves measured by 5 laboratories and by the author at these laboratories were made (Fig 7) The author had measured the electron energies at all the laboratories so that the variations in the results depended only upon the dosimetric technique employed The depths for 80 % and 50 % depth doses (30 MeV 8 × 10 cm) measured by the various laboratories and by the author differed by a maximum of 0 5 cm and 0 4 cm respectively This difference must be regarded as totally acceptable in radiotherapy

Conclusions

Intercomparisons of absorbed dose calibrations at a reference point along the central ray showed very good agreement with ^{60}Co, radiation (8 laboratories were compared the extreme values differed with 3 2 %) and great differences at electron and roentgen radiation (11 laboratories were compared, the extreme values differed with 27 and 23 % respectively) With electron and roentgen radiation the maximum absorbed dose often lies outside the central axis (SVENSSON & HETTINGER 1971) This means that even if different laboratories have carried out uniform absorbed dose calibration at a reference point along the central axis great differences may exist in absolute dose maximum The maximum dosimetric differences between clinics in the Nordic countries may thus be still worse than the figures above indicate

Absorbed dose calibrations of commercial thimble ionization chambers against $FeSO_4$ dosimeters with 11 betatrons and 3 linear accelerators showed that it is possible to use these chambers to establish sufficient uniform dosimetry along the central ray for radiotherapy If the energy is determined in a uniform way

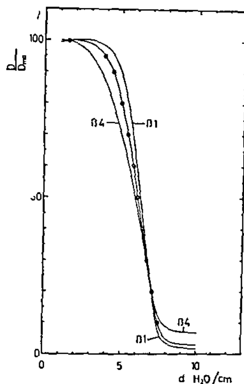


Fig 6

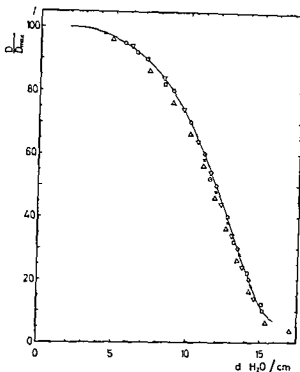


Fig 7

Fig 6 Relative depth dose curves measured at 15 MeV e radiation with 0 1 (p_1) and 1 (p_4) mm Pb foils with Siemens 42 MeV betatron (—) Field size $> \varnothing 12$ cm A somewhat higher energy was set on the instrument panel of the betatron when the thicker foil was used in order to obtain similar electron energy E_0 at the phantom surface A relative depth dose curve with one BBC 35 MeV betatron ○———○ at 15 MeV is also shown

Fig 7 Intercomparisons of depth dose curves measured by the various laboratories and by the author at these laboratories Energy 30 MeV field size 8 × 10 cm The author s curve is a mean of the results from all the laboratories The separate curves agreed however within 0 1 cm The energy was determined by the author at all the laboratories the variations between the various laboratories thus depended only upon different dosimetric techniques
○ author s measurement □ laboratory No 2 ▽ laboratory No 4 △ laboratory No 6 and \ laboratory No 7

≥ Φ 6 cm (Tables 6 and 7) despite the fact that the energy degradation was greater in the former betatron type

The depth dose curves depend upon the method of field shaping LOEVINGER et coll (1961) thus showed that low energy electrons from the collimator tube increased the absorbed dose at 1 cm depth in a water phantom by approximately 40 % compared with an irradiation performed without the tube (30 MeV Φ 6 cm) SVENSSON & HETTINGER (1967) observed a corresponding increase of 10 % with a BBC betatron (15 MeV and 8 × 10 cm) and showed it to be greatest for small field sizes Different collimator constructions may possibly explain that the

95 and 90 per cent depth doses with small field sizes (ϕ 4 cm in Tables 6 and 7 occurred at smaller depths with the BBC betatrons than with the Siemens 42 MeV betatron These depth doses occur however, most often at greater depths *with BBC betatrons for large field sizes* Another cause may be that small field sizes are flattened more with Siemens than with BBC betatrons (homogeneity index 0 8 and 0 6, respectively compare above) and somewhat larger effective field size are thus obtained with the former

SCHULTZ (1969) showed that the depths for 50 % depth dose measured in *different laboratories (25 MeV 10 × 10 cm) differed* by up to 1 5 cm POHLIT s (1961) measurements and the present study showed however, that the differences between depth dose curves from different types of betatrons are considerably less A large part of this difference must therefore be ascribed to variations in energy calibration The given energy however is of less importance for usage of the depth dose curves for radiotherapy *provided that these curves are accurately* known for a given MeV instrument setting

Comparisons between relative depth dose curves measured by 5 laboratories and by the author at these laboratories were made (Fig 7) The author had measured the electron energies at all the laboratories so that the variations in the results *depended* only upon the dosimetric technique employed The depths for 80 % and 50 % depth doses (30 MeV 8 × 10 cm) measured by the various laboratories and by the author differed by a maximum of 0 5 cm and 0 4 cm, respectively This difference must be regarded as totally acceptable in radiotherapy

Conclusions

Intercomparisons of absorbed dose calibrations at a reference point along the central ray showed very good agreement with ^{60}Co , radiation, (8 laboratories were compared the extreme values differed with 3 2 %) and great differences at electron and roentgen radiation (11 laboratories were compared the extreme values differed with 27 and 23 % respectively) With electron and roentgen radiation the maximum absorbed dose often lies outside the central axis (SVENSSON & HETTINGER 1971) This means that even if different laboratories have carried out uniform absorbed dose calibration at a reference point along the central axis great differences may exist in absolute dose maximum The maximum dosimetric differences between clinics in the Nordic countries may thus be still worse than the figures above indicate

Absorbed dose calibrations of commercial thimble ionization chambers against $FeSO_4$ dosimeters with 11 betatrons and 3 linear accelerators showed that it is possible to use these chambers to establish sufficient uniform dosimetry along the central ray for radiotherapy If the energy is determined in a uniform way

(described by SVENSSON & HETTINGER 1971) it thus would be possible to transfer absorbed dose calibrations by thimble ionization chambers between the centres with an uncertainty less than about 2 % with both electron and roentgen radiation

Relative depth doses with roentgen rays from accelerators of the same makes and models agreed within about 1 5 % The curves were dependent on the flattener used

With electron radiation the depths for a given percentage depth dose (e g 95, 90, 80 %) agreed closely for 8 BBC 35 MeV betatrons The standard deviations of the depths were about 0 1 cm for a given energy and field size Significant differences in relative depth doses for different makes and models were observed Different energy degradation of the electrons in the tube windows, scattering foils and in the collimating tubes for the studied betatron makes are probable explanations

Acknowledgements

The author gratefully acknowledges the radiotherapeuts and physicists at the visited places and the technical assistance of Mr B Sjostrom The work was supported by grants from the Swedish Cancer Society

SUMMARY

A measuring program was carried out on betatrons and linear accelerators at 11 laboratories in Denmark Finland Norway and Sweden Great discrepancies existed between the basic dosimetry of the various laboratories It was shown that thimble ionization chambers could be used to transfer absorbed dose calibrations within 2 % between the various centres with both electron and photon radiation The depth dose curves from the different accelerators were compared

ZUSAMMENFASSUNG

Ein Messprogramm fur Elektronenschleudern und Linearacceleratoren von 11 Laboratorien in Danemark Finland Norwegen und Schweden wurde durchgefuhrt Es existieren grosse Unterschiede zwischen der Basisdosimetrie der verschiedenen Laboratorien Es wird gezeigt dass Fingerhut Ionisationskammern verwendet werden konnen um innerhalb von 2 % Kalibrierungen der absorbierten Dosis sowohl fur Elektronen als auch Photonen Strahlung zwischen den verschiedenen Zentren zu ubertragen Die Tiefendosis Kurven von den verschiedenen Acceleratoren werden verglichen

RÉSUMÉ

L auteur a executé un programme de mesures sur des bétatrons et des accélérateurs linéaires dans onze laboratoires situés au Danemark en Finlande en Norvege et en Suede

Il existait de grandes discordances entre les principes de dosimetrie dans ces differents laboratoires Ce travail a montre qu on peut utiliser des chambres d ionisation de a coudre pour transmettre d un centre a l autre les etalonnages de dose absorbee avec une precision de 2 % aussi bien avec le rayonnement electronique qu avec les photons Les doses de courbe en profondeur provenant des differents accelerateurs ont eté comparees

REFERENCES

ALMOND P R The physical measurements of electron beams from 6 to 18 MeV Absorbed dose and energy calibration Phys in Med Biol 12 (1967) 13

— C_λ values for high energy X radiation Phys in Med Biol 13 (1968) 285

— The use of ionization chambers for the absorbed dose calibration of high electron beam therapy units. Int J appl Radiat (1970) 1

BERGER M J and SELTZER S M Quality of radiation in a water medium irradiated with high energy electron beams Paper presented at the 12th International Congress of Radiology Tokyo Japan October 1969

BEWLEY D K The measurement of locally absorbed dose of megavoltage X rays by means of a carbon calorimeter *Brit J Radiol 36 (1963) 865*

BURLIN T E Cavity-chamber theory *In* Radiation dosimetry Second edition Volume I Fundamentals p 331 Edited by F H Attix W C Roesch and E Tochilin Academic Press New York 1968

GREENE D The HPA and AAPM survey of depth-dose data for teleisotope γ rays and mega voltage X rays *In* High energy radiation therapy dosimetry Edited by J S Laughlin Ann N Y Acad Sci 161 (1969) 168

HARDER D Energiespektren schneller Elektronen in verschiedenen Tiefen *In* Symposium on high energy electrons p 26 Edited by A Zuppinger and C Poretti Springer Verlag Berlin 1965

— Einfluss der Vielfachstreuung von Elektronen auf die Ionization in gasgefüllten Hohlraumen Biophysik 5 (1968) 157

HETTINGER G PETTERSSON C and SVENSSON H (a) Displacement effect of thimble chambers exposed to a photon or electron beam from a betatron Acta radiol Ther Phys Biol 6 (1967) 61

— — — (b) Calibration of thimble chambers in a 34 MV roentgen beam Acta radiol Ther Phys Biol 6 (1967) 214

HORSLEY R J PRICE R H SAUNDERS J E and DINGWALL P W *Performance of a 6 MeV* Varian linear accelerator Brit J Radiol 41 (1968) 312

HOSPITAL PHYSICISTS ASSOCIATION (HPA) A code of practice for the dosimetry of 2 to 35 MV X ray and caesium 137 and cobalt 60 gamma ray beams Phys in Med Biol 13 (1969) 1

INTERNATIONAL COMISSION ON RADIATION UNITS AND MEASUREMENTS (ICRU) Report No 12 Certification of standardized radioactive sources ICRU Washington D C 1968

INTERNATIONAL COMMISSION ON RADIATION UNITS AND MEASUREMENTS (ICRU) Report No 14 Radiation dosimetry X Rays and gamma rays with maximum photon energies between 0 6 and 50 MeV ICRU Washington D C 1969

KESSARIS N D Absorbed dose and cavity ionization for high energy electron beams Radiat Res 43 (1970) 288

LOEVINGER R KARZMARK C J and WEISSBLUTH M Radiation therapy with high energy electrons Part I Physical considerations 10 to 60 MeV Radiology 77 (1961) 906

PETTERSSON C Calorimetric determination of the G value of the ferrous sulphate dosimeter with high energy electrons and ^{60}Co gamma rays Arkiv for Fysik 34 (1967) 385

— and HETTINGER G Dosimetry on high energy electron radiation based on the ferrous sulphate dosimeter Acta radiol Ther Phys Biol 6 (1967), 160

PINKERTON A P Comparison of calorimetric and other methods for the determination of absorbed dose *In* High energy radiation therapy dosimetry Edited by J S Laughlin Ann N Y Acad Sci 161 (1969) 63

POHLIT W Standardisierung der Dosismessung bei energiereichen Strahlungen Georg Thieme Verlag, Stuttgart 1961

RASSOW J Beitrag zur Elektronentiefentherapie mittels Pendelbestrahlung Strahlentheraphie 138 (1969) 267

SCHULTZ R J AAPM/HPA survey of high energy electron depth dose data *In* High energy radiation therapy dosimetry Edited by J S Laughlin Ann N Y Acad Sci 161 (1969) 176

SEMPERT M und WIDEROE R Untersuchungen uber Dosimetrie und Ausblendung von 30 MeV Elektronenstrahlen *In* Betatron und Telekobalttherapie S 182 Herausgegeben von J Becker und K E Scheer Springer Verlag Berlin 1958

SHALEK R J and SMITH C E Chemical dosimetry for the measurement of high energy photons and electrons *In* High energy radiation therapy dosimetry Edited by J S Laughlin Ann N Y Acad Sci 161 (1969) 44

SVENSSON H The influence of scattering foils transmission monitors and collimating system on the absorbed dose distribution from 10 to 35 MeV electron radiation Acta radiol Ther Phys Biol 10 (1971) 443

— and HETTINGER G Influence of collimating systems on dose distribution from 10 to 35 MeV electron radiation Acta radiol Ther Phys Biol 6 (1967) 404

— — Dosimetric measurements at the Nordic medical accelerators I Characteristics of the radiation beam Acta radiol Ther Phys Biol 10 (1971) 369

— and PETTERSSON C Absorbed dose calibration of thimble chambers with high energy electrons at different phantom depths Arkiv för Fysik 34 (1967) 377

— — and HETTINGER G Effects on ferrous sulphate dosimeter solution stored in small polystyrene cells *In* Solid state and chemical radiation dosimetry in medicine and biology IAEA Vienna 1967

— — — Commercial thimble chambers for absorbed dose measurements at high energy electron radiation Acta radiol Ther Phys Biol 10 (1971) 504

WEBSTER F W and TSIEN K C *Atlas of radiation dose distributions* Vol I Single field isodose charts IAEA Vienna 1965

WICKMAN G A digitized unit for precision charge measurement on ionization chambers To be published in Acta radiol Ther Phys Biol

LIST OF TRIALS INVOLVING RADIATION THERAPY BROUGHT TO THE NOTICE OF THE INFORMATION OFFICE OF THE COMMITTEE ON CONTROLLED THERAPEUTIC TRIALS OF THE UICC BY JANUARY 1971

Edited by
the Information Office of the Committee on Controlled Therapeutic Trials

An Information Office has been established by the Committee on Controlled Therapeutic Trials (Commission on Clinical Oncology International Union Against Cancer) The Office collects and distributes information on trials planned in progress or terminated whose results have not been published

Members of the Information Office Prof D Schwartz (Chairman) Unite de Recherches *Statistiques de l INSERM 94 Villejuif (France)* Dr R Flamant Institut Gustave Roussy 94 Villejuif (France) Dr A Garin Institute of Experimental and Clinical Oncology Moscow (USSR) Dr J L Hayward Guy s Hospital London (England) Dr G Higgins Veterans Administration Hospital Washington (USA) Dr H Høst The Norwegian Radium Hospital Montebello Oslo (Norway) Dr Y Kenis Institut Jules Bordet Brussels (Belgium) Dr Y Koyama Tokyo First National Hospital Tokyo (Japan) Prof A Ratti Istituto di Radiologia dell Universita di Milano Milan (Italy) Prof G Wagner Statistisches Institut des Deutschen Krebszentrums Heidelberg (Fed Rep Germany)

Information on such trials is collected by the members of the Information Office who are supported in this task by a network of corresponding members

A list of the trials registered by the Office is published systematically This list only gives the information *that is necessary to enable each investigator to have an idea of what is* being done but omits the names and addresses of chief investigators *Physicians may apply to the secretariat of the Office to be given the names and addresses of the chief investigators of the trials they are interested in* The first list has been published in 1969 and the second in 1970 They will be followed by yearly updatings which will consist of

1 A list of the new trials brought to the notice of the Information Office during the past year

2 A list of the trials whose results have been published since the issue of the previous list

These lists and their updatings only give basic information concerning the type of patients and the compared groups The present list concerned only with trials involving radiation therapy has been prepared at the request of a number of radiotherapists It gives detailed information on the radiation technique used

As far as the methodology of trials is concerned the Committee has written a technical report entitled *Controlled therapeutic trials (UICC Technical Report Series—Volume 7* Controlled Therapeutic Trials Geneva 1970 This book can be purchased from International Union Against Cancer P O Box 400 1211 Geneva 2 Switzerland) Besides a summary of methodology of clinical trials the report contains a detailed description of the function of the Information Office and the second list of trials established by the Office

Finally it must be emphasized that the fact that a trial is mentioned in the lists established by the Information Office does not imply that a judgement has been passed upon its methodology For the time being asterisks indicate the trials in which the patients are allocated to treatment groups according to letters of the alphabet or their dates of birth or on an alternative basis since these methods are not truly random

The members of the Information Office are grateful to Dr K Rubinstein Zummer Department of Radiation Therapy Institut Gustave Roussy, Villejuif for reviewing the manuscript They also wish to thank Miss C Folianno for technical assistance

For information apply to the secretary Dr R Flamant Institut Gustave Roussy 16bis Avenue Paul Vaillant Couturier 94 Villejuif France

I *Trials concerned with radiation therapy alone*

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Head and neck							
Irradiation of the tumor	Larynx	Conventional deep roentgen therapy 250 kV HVL 2 5 mm Cu	5 400 R	36	6 × 180 R/T/week (30 fractions)		69 2*
Irradiation of the tumor and the cervical nodes	Larynx Cervical nodes		5 400 R	42	6 × 150 R/T/week (36 fractions)		
Conventional fractionation	Tonsil Upper and mid jugular nodes	23 MeV betatron roentgen rays	4 500—8 500 rad	32—60	3 × 330 rad/week	Trial completed	69—3

Compa ed groups	Target volume	Type of rad ation	Tumor dose	Over all time (days)	Fractiona tion	Remarks	Ref er ence No
Modified frac t o at on (RBC/D)		”	5 300—9 600 rad*	32—60	2 × 190 rad at 2 hour intervals 3 × per week	*Dose supposed to be equiva lent to that gi en in the other group	
Irradiation (3 days/ week)	Tons l soft palate base of tongue tongue with whole neck	Co	5 250—5 9?0 rad	32—38	3 × 350 rad/week (15—17 fractions)	Split course accasionally with a gap of 14—21 days	71—a*
Irrad at on (5 days/ week)			6 000—6 800 rad	30—40	5 × 200 rad/week (30—34 frac t ons)		
Or pharynx T3 Irr diation (ordinary techn que)	Tumor and ubmandi bular lymph nodes	Co	7 000 rad	50	40 × 180 rad		71—b
Irradi t on (low do e rate 2 5 rad/ min)			6 000 rad	6	6 × 1 000 rad		
Irrad ation (normal dose rate 80 rad/ m n) (spl t course)			7 000 ad	60	3 × 1 000 rad 2 × 1 000 rad 2 × 1 000 rad	?0 day interval betv een courses	
Cervix uteri							
⁶⁰Co rad at on 22 MeV radiat on	*Publicati n* ALLT W E C Supervoltage radiation treatment in ad anced cancer of the uter ne cerv x Canad med Ass J 100 (1969) 792						69—41
Sk n							
l-day r ad at on	Tumor	Superfic al roentgen ray	2 000—2 250 R	1	1 × 2 000—2 ?50 R		0—43

These lists and their updatings only give basic information concerning the type of patients and the compared groups. The present list concerned only with trials involving radiation therapy has been prepared at the request of a number of radiotherapists. It gives detailed information on the radiation technique used.

As far as the methodology of trials is concerned the Committee has written a technical report entitled Controlled therapeutic trials (UICC Technical Report Series—Volume 7 Controlled Therapeutic Trials Geneva 1970. This book can be purchased from International Union Against Cancer P O Box 400 1211 Geneva 2 Switzerland.) Besides a summary of methodology of clinical trials the report contains a detailed description of the function of the Information Office and the second list of trials established by the Office.

Finally *it must be emphasized that the fact that a trial is mentioned in the lists established by the Information Office does not imply that a judgement has been passed upon its methodology.* For the time being asterisks indicate the trials in which the patients are allocated to treatment groups according to letters of the alphabet or their dates of birth or on an alternative basis since these methods are not truly random.

The members of the Information Office are grateful to Dr K. Rubinstein Zummer Department of Radiation Therapy Institut Gustave Roussy Villejuif for reviewing the manuscript. They also wish to thank Miss C. Fohanno for technical assistance.

For information apply to the secretary Dr R Flamant Institut Gustave Roussy 16bis Avenue Paul Vaillant Couturier 94 Villejuif France.

I *Trials concerned with radiation therapy alone*

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Head and neck							
Irradiation of the tumor	Larynx	Conventional deep roentgen therapy 250 kV HVL 2.5 mm Cu	5 400 R	36	6 × 180 R/T/week (30 fractions)		69 2*
Irradiation of the tumor and the cervical nodes	Larynx Cervical nodes		5 400 R	42	6 × 150 R T/week (36 fractions)		
Conventional fractionation	Tonsil Upper and mid jugular nodes	23 MeV betatron roentgen rays	4 500—8 500 rad	32—60	3 × 330 rad week	Trial completed	69—3

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Lymphosarcomas reticulum cell sarcomas							
Irradiation of restricted fields	Involved nodes and adjacent nodal regions excluding mediastinum and Waldeyer s ring	* Co or megavoltage roentgen	4 000 rad (midline) 3 500 rad (midline)	28 28	5 fractions/ week (20 fractions)		70—67
Irradiation of extended fields	As first group plus prophylactic irradiation of the lumbar retroperitoneal lymph nodes		+ 3 500 rad (midline)	28		*Preferably not later than 3 weeks after completing treatment above the diaphragm	
Neurology							
Cerebral metastases							71—c
Irradiation (one session)	The entire head	Co	1 000 rad (midline)	1	1 × 1 000 rad		
Irradiation (conventional fractionation)			3 000 rad (midline)	14	12 × 250 rad		
Miscellaneous							
Children under the age of 20 Sarcoma without pulmonary metastases (±chemotherapy) Control						Prophylactic radiation of the lung irradiation of one lung the opposite lung being used as a control	71—d
Irradiation	One lung (+ carina and all of the trachea)	Supervoltage	1 500 rad	12			

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
4 day irradiation			4 000 R	4	4 × 1 000 R		
8 day irradiation		,,	4 800 R	9	8 × 600 R (6 fractions/week)		
Hodgkin's disease							
Children and adults Stages I & II							69—197
Irradiation of involved fields	*Publications* NICKSON J J Hodgkin's disease clinical trial Cancer Res 26 (1966) 1279						
Irradiation of extended fields	NICKSON J J and HUTCHISON G B Hodgkin's disease clinical trial *In* Sixth National Cancer Conference Proc p 77 J B Lippincott Co Philadelphia 1970						
	STRUM S B HUTCHISON G B PARK J K and RAPPAPORT H Further observations on the biologic significance of vascular invasion Cancer 27 (1971) 1						
	HUTCHISON G B Anatomic patterns by histologic type of localized Hodgkin's disease Abstracts Third International Congress of Lymphology p 1 1970 Edited by J N Gruwez						
	HUTCHISON G B Anatomic patterns by histologic type of localized Hodgkin's disease Submitted for publication Lymphology 1970						
Age 14—65 Previously untreated patients							71—2
Irradiation of involved fields	Clinically involved lymph nodes	Co	4 000 R	28	5 × 200 R/T/week (20 fractions)		
Irradiation of extended fields	Clinically involved areas + clinically uninvolved surrounding areas on the same side of the diaphragm		4 000 R	28	5 × 200 R/T/week (20 fractions)	Peripheral and mediastinal areas	
			3 900 R	42	5 × 130 R/T/week (30 fractions)	Whole abdomen	

Compared groups	Target volume	Type of radiation	Tumour dose	Over all time (days)	Fractionation	Remarks	Reference No.
		(1 MeV or ⁶⁰Co or in excess of this energy)					
—	—	—					
Oesophagectomy Irradiation (1)	Thoracic oesophagus	Co	2 000 rad (1)	5	5 × 400 rad day	Trial not completed	71—e
Preoperative irradiation — oesophagectomy (2)	"	"	5 000 rad (2)	28	20 × 250 rad day		
Colon, rectum							
Surgery Preoperative irradiation — surgery	Rectum	Co	500 rad	1	500 rad in one session		69—34
Surgery Preoperative irradiation — surgery	*Publication*: Roswit B, Higgins G A and Keehn R J: A controlled study of preoperative irradiation in cancer of the sigmoid colon and rectum. Preliminary Report. Radiology 97 (1970) 133						69—35
Cervix uteri							
Stage IB Hysterectomy + lymph node dissection							69—44
Radium — hysterectomy + lymph node dissection		Radium					
Radium + radical surgery		Radium					69—45
Radium + 31 MeV betatron radiation	Pelvic lymph nodes up to bifurcation of aorta	Radium + 31 MeV betatron roentgen rays	4 000 R	30—35	200 R/session		

II Trials concerned with the combination of radiation therapy with other treatments

1 Radiation therapy plus surgery

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Head and neck							
Preoperative irradiation + surgery	Hypopharynx + cervical node areas	^{60}Co	5 500 rad	30	5 × 250 rad/week	Trial completed not yet published	69—4
Surgery + postoperative irradiation	Tumor bed + cervical node areas						
Lung							
Surgery (lobectomy pneumonectomy)							69—13
Preoperative irradiation + surgery	Tumor + nodes (8 cm × 15 cm)	^{60}Co	5 500 rad	25 50	27 × 200 rad/daily 11 × 500—600 rad (every 5 days)	Possibility of administering only 3 500 rad to nodes	
Curative lobectomy — No further treatment						Randomization before operation	71—f
Curative lobectomy — Irradiation	Mediastinum (10 cm × 15 cm)	^{60}Co	6 000—6 500 rad	42	5 fractions/week	Irradiation begins 15—30 days after surgery	
Curative pneumonectomy — No further treatment							
Curative pneumonectomy — Irradiation							
Oesophagus							
Surgery							70—21
Preoperative irradiation + surgery	Mediastinum	Roentgen or gamma beam of radiation	2 000 rad	5	400 R/T daily		

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractiona tion	Remarks	Ref er ence No
	bladder + obturator hypogastric and sacral nodes (8 cm × 10 cm)					wall does not exceed 200 rad	
Stage III							69—61
Total cystectomy							
Irrad at on	Primary tumor	Co	5 500 rad	28	5 × 275 R/T/week		
Preoperative irrad a tion + total cystectomy			4 500 rad		5 × 225 R/T/week		
Kidney							
M0							70—36
Nephrectomy							
Preoperative irradia tion + nephrectomy	Kidney	Linear accelerator or Co	3 000 rad	18—21	5 × 200 rad/week		
Breast							
Stages I & II							69—81
Standard mastectomy + axillary lymph node d ssection							
Standa d mastecto-my + axillary lymph node d ssection + r ad ation	*P rt 4*	200 kV					
	Thorac c wall (skin flaps)	2 mm Cu FSD 50 cm	3 600 R		9 × 400 R (6/week)		
	Supraclavi cular fossa		3 600 R	28—35	9 × 400 R (6/week)		
	Axilla		1 800 R		9 × 200 R (6/week)		
	Pa t B	Co					
	Sup a nfra clavicular reg ons and ax lla Parasternal egion		6 000 rad maximum	28	5 × 300 R/week (20 sessions)		

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Corpus uteri							
Stages I & II							
Standard treatment							69—49
Standard treatment + 31 MeV betatron radiation	Pelvic lymph nodes	31 MeV betatron roentgen rays	4 000 R	30—40	200 R/day	*Standard treatment* *Stage I* Primary hysterectomy oophorectomy vaginal radium application Stage II Primary radium packing followed 6 weeks later by hysterectomy oophorectomy vaginal radium application	
Ovary							
Stages I & II							69—52
Surgery + irradiation	Whole pelvis	^{60}Co or 31 MeV betatron roentgen rays	5 000 R	35—40	200—300 R/session		
Surgery + irradiation + instillation of ^{198}Au			3 000 R	25—30			
Bladder							
Radical cystectomy							71—8
Preoperative irradiation + radical cystectomy	Posterolateral wall of urinary	^{60}Co	2 000 rad	4	4 × 500 rad	The dose to the anterior abdominal	

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
	bladder + obturator hypogastric and sacral nodes (8 cm × 10 cm)					wall does not exceed 200 rad	
Stage III Total cystectomy							69—61
Irradiation	Primary tumor	Co	5 500 rad	28	5 × 275 R/T/week		
Preoperative irradiation + total cystectomy			4 500 rad		5 × 225 R/T/week		
Kidney M0 Nephrectomy							70—36
Preoperative irradiation + nephrectomy	Kidney	Linear accelerator or Co	3 000 rad	18—21	5 × 200 rad/week		
Breast Stages I & II Standard mastectomy + axillary lymph node dissection							69—81
Standard mastectomy + axillary lymph node dissection + irradiation	*Part A* Thoracic wall (skin flap)	200 kV 2 mm Cu FSD 50 cm	3 600 R		9 × 400 R (6/week)		
	Supraclavicular fossa		3 600 R	28—35	9 × 400 R (6/week)		
	Axilla		1 800 R		9 × 200 R (6/week)		
	Part B Supra and infraclavicular regions and axilla Parasternal region	Co	6 000 rad maximum	28	5 × 300 R/week (20 sessions)		

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Simple mastectomy ± irradiation Halsted or extended mastectomy ± irradiation	*Publication* FORREST A P M, CLEAVE L N, ROBERTS M M et coll. A controlled trial of conservative treatment for early breast cancer. Proc Roy Soc Med 63 (1970) 107						69—82
T3 N0 N1							69—83*
Preoperative irradiation + radical surgery	Breast and axillary nodes	250 kV	3 600 R (skin dose)	28	3 × 300 R/week (skin dose)		
	Infra and supraclavicular nodes		3 900 R (skin dose)	14	6 × 300 R/week (skin dose)		
Radical surgery + postoperative irradiation	Scar region		4 000 R	24	6 × 200 R/TD/wk		
	Axillary, infra and supraclavicular nodes						
T1 T2 N0 N1 M0							69—84
Simple mastectomy + postoperative irradiation	Chest wall, axilla, supra and infraclavicular, internal mammary node areas					This protocol does not simply compare 2 forms of surgery but 2 treatment regimes which both involve surgery + postoperative irradiation	
Radical mastectomy + postoperative irradiation	Node areas only						
Halsted + postoperative irradiation	Nodes	200 kV	3 000 R	98*		*3 courses of 2 wks each 4 week a interval between courses	70—38*
Pre operative irradiation + Halsted + post operative irradiation	Tumor		2 000 R	21	10 × 200 R		
	Nodes		3 000 R		10 × 300 R		
	Nodes		3 000 R	23	10 × 300 R		

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractiona tion	Remarks	Ref er ence No
Pre-operat e irra diation + mastec tomy	Tumor Supra and infraclavi cular parasternal node areas	^{60}Co	6 000 R 5 000 R	28		4 year survival 46	70—38 b
Mastectomy + post operat ve irrad ation	Supra and infracla i cular parasternal node areas		5 000 R			44	
Halsted + post operative i adiation	Supra and infracla i cular parasternal node areas Axilla		4 000 R 5 000 R			47	
Sk n							
Truncus —melanoma Stage I Local exc sion of the p imary tumor							70—45
Local exc s on of the p imary tumor + local irradiat on of the primary tumor	Pr mary tumor	Radium mould or superfic al roentgen rays	4 000—5 000 rad	4—5 5—6	Continous 6 fractions		
B ne							
O t o arco a of long bon s—M0 Tr atment of prim y l ons (i r d at on and/o u g ry)	Aff cted bone from jo nt t ll 10 cm above cl nically affected ar a	Co or megavolta ge	7 000 r d	about 49	1 000 rad/ week (35 sessions)		70—69
T tm nt of p nary l s ons +						P ophylactic irradiat on	

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
systematic irradiation of lungs	Both lungs		1 750 rad	about 12	875 rad/week (10 sessions)	of pulmonary metastases begins 4 weeks after treatment of primary lesions	
Miscellaneous							
Thyroid—T0 to T3 N0 to N3 M0 Surgery							71—1
Surgery + postoperative irradiation	Both cervical regions and mediastinum	^{60}Co	5 000—6 200 rad	35—44	25—31 sessions		
	One cervical region and mediastinum		5 500—7 000 rad	38—49	28—35 sessions		

2 *Radiation therapy plus hormone therapy surgery as an endocrine therapy*

Prostate							
Option 1 Irradiation	Pelvis External iliac and obturator nodes	Linear accelerator or ^{60}Co	7 000—7 500 rad	47—54	5 × 200 rad/week		69—59
Endocrine therapy							
Option 2 Irradiation Irradiation + endocrine therapy							
Option 3 Endocrine therapy Endocrine therapy + irradiation							

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Breast							
Irradiation	Tumor and regional lymph node areas	250 kV	5 400 R	35			69—89
Irradiation + oophorectomy							
Irradiation + roentgen castration	Pelvis		1 400 R	4	350 R/T daily		

3 *Radiation therapy plus chemotherapy*

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Head and neck							
Oropharynx, hypopharynx							71—1
Irradiation alone	Tumor and node areas	Co	Not yet determined			Trial in project	
Bleomycin + irradiation							
T4							69—5
Cobalt irradiation	Tumor	Co	3 000—6 000 rad	15	5 × 300 rad/week	Trial completed not yet published	
Methotrexate (I.A.) + irradiation		or brachytherapy					
Irradiation	Tumor and nodes	Co	5 400—6 000 rad	42	5 × 200 R/week		69—6*
Methotrexate + irradiation							
T3 T4 N0 to N3 T1 T2 N2 to N3							69—7

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
systematic irradiation of lungs	Both lungs		1 750 rad	about 12	875 rad/week (10 sessions)	of pulmonary metastases begins 4 weeks after treatment of primary lesions	
Miscellaneous							
Thyroid—T0 to T3 N0 to N3 M0 Surgery							71—1
Surgery + post operative irradiation	Both cervical regions and mediastinum	^{60}Co	5 000—6 200 rad	35—44	25—31 sessions		
	One cervical region and mediastinum		5 500—7 000 rad	38—49	28—35 sessions		

2 *Radiation therapy plus hormone therapy; surgery as an endocrine therapy*

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Prostate							
Option 1							69—59
Irradiation	Pelvis External iliac and obturator nodes	Linear accelerator or ^{60}Co	7 000—7 500 rad	47—54	5 × 200 rad/week		
Endocrine therapy							
Option 2 Irradiation							
Irradiation + endocrine therapy							
Option 3 Endocrine therapy							
Endocrine therapy + irradiation							

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Irradiation	Tumor (8 cm × 15 cm)	Co	5 800 R/T	36	5 sessions/week (22 fractions)		71—n
Irradiation + 5 fluorouracil							
Irradiation	Lung + hilar node area (10 cm × 12 cm)	Co	4 000—6 000 rad	90	5 × 200—300 R/week		69—22
Irradiation + cyclophosphamide							
Irradiation	Tumor and mediastinum	Co	4 500 R	4?	5 × 150 rad/week		69—23*
Cyclophosphamide + irradiation						15-day interval between chemotherapy and irradiation	
Irradiation	Lung and mediastinum	31 MeV betatron gamma rays	4 000 rad 6 000 rad	28—35 35—42	5 × 200 rad/week	a) Oat cell carcinoma b) Squamous cell carcinoma	70—18
Irradiation + cyclophosphamide							
T2 to T4 N0 N1 Nx M1b Irradiation	Lung + hilar node area (10 cm 12 cm)	Co or high energy radiation	4 000 rad	90	5 × 200—300 R/week		70—16
Irradiation + 5 fluorouracil + cyclophosphamide							

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Irradiation	Depending on site	^{60}Co	5 000—8 000 rad	35—70	1 000 rad/week		
Methotrexate (given systematically by intravenous injection) + irradiation							
Buccal mucosa							71—1
Irradiation	Cheek and neck	^{60}Co	6 500 rad	42	5 sessions/week (30 fractions)		
Methotrexate intravenous + irradiation							
Methotrexate *intraarterial + irradiation*							
Methotrexate intraarterial followed by leucovorin rescue + irradiation							
Tonsils and mouth							71—11
Irradiation		^{60}*Co*	*3 500*—5 000 R			Trial in project	
Irradiation + methotrexate + vinblastine + hydroxyurea							
Lung							
External irradiation	Lung and mediastinum	^{60}Co	*3 000 rad*	14	5 × 300 R/T/week		69—20
External irradiation + podophyllic acid							
Cobalt irradiation	*Publication* Cox P A randomized study of irradiation and vinblastine in lung cancer Cancer 26 (1970) 804						69—21*
Cobalt *irradiation* + vinblastine							

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractiona tion	Remarks	Ref er ence No
Oesophagus							
Ist irrad at on (a) + systematic 2nd irradiation (b) ± chemotherapy	Tumor	Co or betatron photons	5 700 rad	53	a) 2 × 800 rad at 48 hour interval b) 3 × 300 rad/week	*Dose equiva lent to *3 000 rad in con ventional fractionation	69—25
Ist i radiation (a) + t reque t 2nd irradiation (b) ± chemotherapy			3 000—5 700 rad		a) b) At request		
Irrad ation	Oesophagus Med ast nal bilateral supraclavi cular areas and coeliac r gion followed by oesophagus	Co or h gh energy photons	4 000 rad + 2 000 ad	28 + 14 (42)	20 × 200 rad + 10 × 200 rad		71—k
Methotrexate + irradiation							
Cer ix uter							
Stage III Age 35—59							69—46
Irradiat on	Whole pelv s	Co	4 000 rad	28—min mum 56	5 days/week		
I radiat on + chromomycin A3							
T3 Nx M0 Age 35—59 W th ureter compr ss on							0—29
I radiation	Whole pelv	Co or l near accele ator (10 MeV)	5 000 rad	35—minimum 56	5 days/week		
I radi t on + 5-flu rou ac l + cyclophospham de + m tom c n C + chromomycin A3							

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Limited disease							70—6—7
Irradiation	Tumor + regional nodes (hilum and mediastinum)	^{60}Co or orthovoltage	4 000—5 000 rad	28—42	5 × 150—200 rad/week	Patients previously treated (surgery chemotherapy) or not)	
Cyclophosphamide							
Irradiation + cyclophosphamide (simultaneously)							
Irradiation (one course) + cyclophosphamide	Lung (mediastinal nodes may be included in the field)	^{60}Co or betatron photons	6 000 rad*	42	800—1 000 rad/week	*5 500 rad if no correction for air	69—24
Irradiation (three courses) + cyclophosphamide			3 × 2 000 rad**	154		**2 month interval between courses	
Irradiation of involved fields ± cyclophosphamide	Lung and mediastinum	^{60}Co	5 000 rad	35—42	1 000 rad/week		70—17*
Irradiation of extended fields ± cyclophosphamide	+ cervical and supraclavicular node areas		4 000 rad		1 800 rad/week		
Irradiation + placebo	Lung	Supervoltage or orthovoltage	5 000 R	56	5 × 200 R/week	234 patients included in study trial completed manuscript in final draft	70—19
Irradiation + procarbazine							
Irradiation + hydroxyurea							

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fract ona tion	Remarks	Ref er ence No
Oesoph gus							
1st irrad ation (a) + systematic 2nd irradiat on (b) ± chemotherapy	Tumor	Co or betatron photons	5 /00 rad	53	a) 2 × 800 rad at 48-hour interval* b) 3 × 300 rad/week	*Dose equiva lent to 3 000 rad in con ventional fractionation	69—25
1st irrad at on (a) + at request 2nd irradiation (b) ± chemotherapy			3 000—5 /00 rad		a) b) At request		
Irradiat on	Oesophagus Mediastinal bilateral supraclav cular areas and coeliac region followed by oesophagus	Co or high energy photons	4 000 rad + 2 000 rad	28 + 14 (42)	20 × 200 rad + 10 × 200 rad		71—1
Methotrexate + irradiation							
Cervix uteri							
Stage III Age 35—59							69—46
Ir adiat on	Whole pelvis	Co	4 000 rad minimum	28—56	5 days/week		
Ir adiation + chromomycin A3							
T3 Nx M0 Age 35—59 With uret r c mp ssion							70—29
Irrad ati n	Whol pelv s	Co or l near accelerator (10 MeV)	5 000 rad minimum	35—56	5 days/week		
Irr diat on + 5-flu rourac l + cy loph spham d + m tomyc n C + chromomy in A3							

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Ovary							
Irradiation	Abdomen and pelvis or pelvis only	^{60}Co 2 MeV	3 500 rad	49	5 × 100 rad/week	60 patients included in study trial completed study being analysed	69—54
Chlorambucil							
Irradiation + chlorambucil							
Kidney							
Wilms tumor Children with pulmonary metastases							69—64
Irradiation + vincristine	Both lungs and mediastinum	250 kV	1 200—2 000 rad	10—15	150 rad daily		
Irradiation + actinomycin D							
Irradiation + vincristine + actinomycin D							
Breast							
T3 T4						If disease is not improved or is aggravated hormone therapy is administered	69—90
Local irradiation	Whole breast	Deep roentgen therapy (HVL 3 5 mm Cu)	3 800—4 600 rad	26—32			
	Axillary supraclavicular internal mammary node areas		3 400—4 500 rad	25—32	5 days/week		
Vinblastine (intra arterial) + irradiation							
Chronic leukaemia							71—
Prednisone							
Irradiation	Total body	^{60}Co	200 R*	20—	2—4 × 5	*Responders o	

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractiona tion	Remarks	Ref er ence No
Treatment determined optimal by each investigator		? M V		40*	rad/week depending on platelet count	may receive serial courses of total body irradiation as required for recurrent symptomatic disease	
Hodgkin s disease							
Irradiation*	Clinically involved areas	Co or megavoltage Roentgen	4 000— 4 500 rad	28	5 × 200 rad/week	Randomization after irradiation	69— 137
	Regional areas		3 500 rad	25— 28			
+ No further treatment Vinblastine (2 years)						Inclusion of patients over	
Stage I II & III Irradiation	Involved lymph nodes	250 kV	Depends on the anatomic localisation and clinical advancement of disease description of technique given in the Pol Rev Radiol nucl Med 31 (1967) 842				69— 138*
Irradiation + nitrogen mustard							
Stage III Chemotherapy = vinblastine + nitrogen mustard							69— 139
Chemotherapy + irradiation of involved fields	All involved areas Above diaphragm Below diaphragm Spleen	High energy radiation 1 MeV minimum	3 500— 4 000 rad	25— 35*		Several or all areas should be started simultaneously if feasible total may not exceed 105 days	
Chemotherapy + radiation of extended fields	Lymph bearing areas Inverted Y (below						

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Ovary							
Irradiation	Abdomen and pelvis or pelvis only	^{60}Co 2 MeV	3 500 rad	49	5 × 100 rad/week	60 patients included in study trial completed study being analysed	69—54
Chlorambucil							
Irradiation + chlorambucil							
Kidney							
Wilms tumor Children with pulmonary metastases							69—64
Irradiation + vincristine	Both lungs and mediastinum	250 kV	1 200—2 000 rad	10—15	150 rad daily		
Irradiation + actinomycin D							
Irradiation + vincristine + actinomycin D							
Breast							
T3 T4						If disease is not improved or is aggravated hormone therapy is administered	69—90
Local irradiation	Whole breast	Deep roentgen therapy (HVL 3 5 mm Cu)	3 800—4 600 rad	26—32			
	Axillary supraclavicular internal mammary node areas		3 400—4 500 rad	25—32	5 days/week		
Vinblastine (intra arterial) + irradiation							
Chronic leukaemia							
Prednisone							71—
Irradiation	Total body	^{60}Co	200 R*	20—	2—4 × 5	*Responders o	

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
bazine nitrogen mustard vincristine Chemotherapy combined with radiation therapy							
1 — Procarbazine							
2 — Irradiation	All glandular areas		3 500 rad				
3 — Vinblastine							
Bone							
Ewing sarcoma							69—
Irradiation	The whole of the affected part of the skeleton	Co or megavoltage roentgen	4 000—6 000 rad	28—42	5 × 200 rad/week	Randomization at mid course of irradiation	155
Irradiation + melphalan + cyclophosphamide							
Neurology							
Prednisone						54 patients	69—
Prednisone + irradiation + placebo maintenance	Cerebral metastases	Co	4 000 rad	28	5 × 200 rad/week	included trial completed manuscript accepted by Amer J Roentgenol	157
Prednisone + irradiation + prednisone maintenance							

4 *Radiation therapy plus oxygenotherapy*

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Head and neck							
Irradiation in air	Tumor and lymph node areas	Supervoltage (linear accelerator or Co)	3 750—4 500 rad	19	3 × weekly		70—1
Irradiation in high tension oxygen							

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
	diaphragm)		3 000—3 500 rad	25—32			
	Mantle (above diaphragm)						
	Spleen +		2 500—3 000 rad	21—32			
	Involved areas**		3 500—4 000 rad	25—35		**From the start of irradiation to lymph bearing areas	
Irradiation of extended fields							
Irradiation of extended fields + chemotherapy							
Stage III B							71—P
Radiation therapy alone radical irradiation above and below the diaphragm	1 — Above the diaphragm	* Co					
	a) involved regions		a) 4 000 rad*	28		*Midplane	
	b) prophylactic regions		b) 3 500 rad*	28			
	2 — Below the diaphragm lumbar region and spleen					Interval between 1 2 and 3 4 to 6 wks	
	3 — Iliac and inguinal regions						
Chemotherapy alone Prednisone procar							

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractiona tion	Remarks	Ref er ence No
baz ne n trogen mustard vincrist ne Chemotherapy comb ned with ad tion therapy 1 — Procarbaz ne 2 — Irradiat on 3 — Vinblastine	All glandu lar areas		3 500 rad				
Bone							
Ew g sarcoma Irrad tion	The whole of the affec ted part of the skeleton	Co or megavol tage roentgen	4 000— 6 000 rad	28— 42	5 × 200 rad/week	Randomiza t on at mid-course of irradia tion	69— 155
Irrad ation + melphalan + cyclo-phosphamide							
Neurology							
Prednisone							
Predn sone + irra d ation + placebo ma ntenance	Cerebral metasta es	Co	4 000 rad	28	5 × 200 rad/week	54 pat ents included trial com pleted ma nuscript accepted by Amer J Roentgenol	69— 157
Predn sone + irra d ation + prednisone ma ntenance							

4 *Radiation therapy plus oxygenotherapy*

Head and neck							
I r d at on n a r	Tum r and lymph node a eas	Super voltage (linear acc lerator r Co)	3 750— 4 500 rad	19	3 × weekly		70— 1
Ir ad at on n high I n on xygen							

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Irradiation	Larynx	^{60}Co	6 000 rad	41			70—2*
Irradiation + hyperbaric oxygen			4 800 rad	30—35	12 × 400 rad		
Lung							
Irradiation in air	Tumor + Nodes (<150 cm²)	Super voltage (linear accelerator or ^{60}Co)	3 600 rad	19	Twice weekly		70—4
Irradiation in high tension oxygen							
Irradiation	Tumor or tumor bed with mediastinum	^{60}Co	4 800 rad	30—35	12 × 400 rad	Inoperable cases or residual tumor after lobectomy or pneumonectomy	70—5
Irradiation + hyperbaric oxygen							
Cervix uteri							
Stages II, III and IV Irradiation		^{60}Co or linear accelerator				Trial in project	69—42
Irradiation + oxygen inhalation (atmospheric and hyper hyperbaric O_2)							
Stages III and IV Irradiation in air	Pelvis	Super voltage ± radium (linear accelerator or ^{60}Co)	3 500—4 250 rad	21—28	2—3 × weekly		70—28
Irradiation in high tension oxygen							

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Bladder							
Irradiation	1st step Whole pelvis	Co	3 500 rad	21	5 × weekly (16 fractions)		69—60
	2nd step Bladder		1 500 rad	1	1 fraction	1st & 2nd steps	
Irradiation + orthobaric oxygen							
Irradiation in air	Pelvis	Supervoltage (linear accelerator or Co)	3 600 rad	19	Twice weekly	Patients with tumor and nodes confined to pelvis blood urea not higher than 100 mg per cent	70—34
Irradiation in high tension oxygen							
Irradiation	Bladder	Co	6 000 rad	42		Patients with recurrent multifocal lesions	70—35
Irradiation + hyperbaric oxygen			4 800 rad	30—35	12 × 400 rad		
Neurology							
Astrocytoma operated cases (Grade III)							70—70
Irradiation	Brain	Co	4 800 rad	30—35	12 × 400 rad		
Irradiation + hyperbaric oxygen							

5 *Radiation therapy plus surgery plus hormone therapy surgery as an endocrine therapy*

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Breast							
T2 N1 M0							70—41
Radical mastectomy							
Radical mastectomy + testosterone +	Scar region	250 kV	4 000 R	24	5 × 200 R/week		

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
irradiation	Axillary infra and supraclavicular nodes						
Surgery + irradiation +							69—92
Series I No further treatment Ovarian irradiation	Pelvis	^{60}Co	2 000 rad	5	5 × 400 rad	Series I Stages II and III Age 35—44	
Series II No further treatment Ovarian irradiation Ovarian irradiation + prednisone						Series II Stages I II and III Age 45—59 In these series urine is collected for discriminant function	
Series III As Series II						Series III Stages I II and III Age >60	
Menstruating women Stages IIIA and IIIB Radical mastectomy + oophorectomy + prednisolone ± thiotepa						Preliminary report published in 1963 All Union Cancer Conference	69—93*
Preoperative irradiation + Radical mastectomy +	Breast and axilla	Gamma irradiation	4 000—5 000R	28—35	200—300 R/day	Publication in preparation at present	
Post operative irradiation	Retrosternal space (between 1st & 7th		4 000—5 000 R	35—42			

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
	costal cartilages) infra and supraclavicular spaces						
+ Oophorectomy + prednisolone							
Pre and post operative irradiation + radical mastectomy	The same as 2nd group						

6 *Radiation therapy plus surgery plus chemotherapy*

Lung							
T1 N0 M0							
Lobectomy							70—20
Lobectomy + cyclophosphamide + external irradiation	Lung and mediastinum	High energy radiation	*5 000 R*	*56*	4 × 200 R/week		
Cervix uteri							
Stage II Age 35—59							
Surgery + irradiation	Whole pelvis	Co	3 000 rad maximum	about 21	5 × weekly		69—47
Surgery + irradiation mitomycin C							
T2 Nx M0 Age 35—39							70—30

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Radical surgery + irradiation Radical surgery + irradiation + 5 fluorouracil cyclophosphamide mitomycin C chromomycin A3	Whole pelvis	⁶⁰Co	4 000 rad	28	5 × 200 rad/week		
Ovary							
Surgery + postoperative irradiation + at request chemotherapy Surgery + postoperative irradiation + immediate chemotherapy	1966—1967 Whole pelvis	Roentgen (6 MeV)	1966 4 000 rad (mid plane) 1967 5 000 rad (mid plane)	49	4 × 150 rad/week (33 fractions)	Chemotherapy = Cyclophosphamide vincaleucoblastine 5 fluorouracil administered subsequently	69—53
	1968—1969 Whole pelvis		5 000 rad (mid plane)	49			
	Upper abdomen up to diaphragm inclusive		2 500 rad (mid plane)		5 × 75 rad/week (33 fractions)		
	1970 Whole pelvis		5 000 rad (mid plane)	49	5 × 150 rad/week (33 fractions)		
	Para aortic chain up to Th12		5 000 rad (mid plane)				
Stage III Surgery + irradiation + at request chemotherapy	Total abdomen	Co	5 000 R*	30—40	5 × 300 R/week	*Kidney shielding after 2 000 R	70—32
Surgery + irradiation + immediate thio tepa			3 000 R	25—30			

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No.
Bladder							
Surgery — Placebo / 5 fluorouracil							[illegible]9—62
Preoperative irradiation + surgery — Placebo / 5 fluorouracil			4 500 rad	28—32			
Kidney							
Children with Wilms tumor. Well encapsulated localized lesions							71—[illegible]
Surgery + actinomycin D							
Surgery + actinomycin D + postoperative irradiation	Flank (tumor bed)	Megavoltage or the equivalent	1 800—4 000 rad*	12—28	5—6 × weekly (1 000 rad/week)	Depending on age (Average 3 000)	
Children with Wilms tumor. Tumor extending beyond kidney but completely resected. Residual nonhematogenous tumor confined to abdomen							71—[illegible]
Surgery + postoperative irradiation	Flank or entire peritoneal cavity depending on extent of involvement noted surgically	Megavoltage or the equivalent	1 800—4 000 rad*	12—28	5—6 × weekly (1 000 rad/week)	*Depending on age total dose to remaining kidney not to exceed 1 500 rad dose to the entire liver not to exceed 3 000 rad in 25—28 days	
+ [illegible]							

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Radical surgery + irradiation Radical surgery + irradiation + 5 fluorouracil cyclophosphamide mitomycin C chromomycin A3	Whole pelvis	^{60}Co	4 000 rad	28	5 × 200 rad/week		
Ovary							
Surgery + postoperative irradiation + at request chemotherapy Surgery + postoperative irradiation + immediate chemotherapy	1966—1967 Whole pelvis	Roentgen (6 MeV)	1966 4 000 rad (mid plane) 1967 5 000 rad (mid plane)	49	4 × 150 rad/week (33 fractions)	Chemotherapy = Cyclophosphamide vincaleucoblastine 5 fluorouracil administered subsequently	69—53
	1968—1969 Whole pelvis Upper abdomen up to diaphragm inclusive		5 000 rad (mid plane) 2 500 rad (mid plane)	49	5 × 75 rad/week (33 fractions)		
	1970 Whole pelvis Para aortic chain up to Th12		5 000 rad (mid plane) 5 000 rad (mid plane)	49	5 × 150 rad/week (33 fractions)		
Stage III Surgery + irradiation + at request chemotherapy Surgery + irradiation + immediate thiotepa	Total abdomen	^{60}Co	5 000 R* 3 000 R	30—40 25—30	5 × 300 R/week	*Kidney shielding after 2 000 R	70—39

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractiona tion	Remarks	Ref er ence No
Castrat on + irra d ation + cyclophos phamide							
Series III (T0 to T4 N1 to N2 M1)							
Castrat on + irra diation + cyclo- phosph mide	Inguinal iliac and para aortic node areas	Super voltage	4 500 rad	35—42	1 000 rad/ week		
	Mediastinum		3 000 rad	21—28		If one single pulmonary metastas s 3 000 rad *2 subgroups A = no metastases in parenchymal organs B = *metas* tases in parenchymal organs no rad ation therapy	
	Left supra clavicular area		3 000 rad				
	Involved organs		3 000—4 000 rad				
Ca trat on + irra diat on + cyclo- pho phamide + methylhydrazine							
Ge minat ve tumors othe than pure sem noma							71—\
S ie I (T0 to T4 N0 M0)							
Ca t ati n + irra d at on	Inguinal il ac and para aort c node areas	Super oltage	4 500 rad	35—42	800—1 000 rad/week		
Castrat on + irra d ation + act no- myc n D							
Ser e II (T0 to T4 N1 to N2 M0)							
Ca t at on + rra d ation — ctino-	Ingu nal liac and	Super voltage	5 000 rad	35—42			

Compared groups	Target volume	Type of radiation	Tumor dose	Overall time (days)	Fractionation	Remarks	Reference No
Children with Wilms tumor Metastatic tumor							71—u
Surgery + post-operative irradiation + vincristine + actinomycin D	Both lungs	Megavoltage or the equivalent	1 400 rad				
	Liver*		3 000 rad	25—28		*Remaining kidney must be protected	
	Brain, bones, lymph nodes**					**Doses comparable to those delivered to the liver	
Pre-operative vincristine + surgery + post-operative irradiation + vincristine + actinomycin D							
Testis							
Seminoma Series I (T0 to T4 N0 M0)							71—v
Castration + irradiation	Inguinal, iliac and para-aortic node areas	Supervoltage	3 000 rad	21—28	1 000 rad/week		
Castration + irradiation + cyclophosphamide							
Series II (T0 to T4 N1 to N2 M0)							
Castration + irradiation	Inguinal, iliac and para-aortic node areas	Supervoltage	3 000—4 500 rad	35—42			
	Mediastinum		3 000 rad	21—28			
	Left supraclavicular area		3 000 rad				

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Castration + irradiation + cyclophosphamide							
Series III (T0 to T4 N1 to N2 M1)							
Castration + irradiation + cyclophosphamide	Inguinal iliac and para aortic node areas	Super voltage	4 500 rad	35—42	1 000 rad/week		
	Mediastinum		3 000 rad	21—28		If one single pulmonary metastasis 3 000 rad	
	Left supra clavicular area		3 000 rad			*2 subgroups A = no metastases in parenchymal organs B = metastases in parenchymal organs no radiation therapy	
	Involved organs		3 000—4 000 rad				
Castration + irradiation + cyclophosphamide + methylhydrazine							
Germinative tumors other than pure seminoma							71—w
Series I (T0 to T4 N0 M0)							
Castration + irradiation	Inguinal iliac and para aortic node area	Super voltage	4 500 rad	35—42	800—1 000 rad/week		
Castration + irradiation + actinomycin D							
Series II (T0 to T4 N1 to N2 M0)							
Castration + irradiation + actino-	Inguinal iliac and	Super voltage	5 000 rad	35—42			

Compared groups	Target volume	Type of radiation	Tumor dose	Overall time (days)	Fractionation	Remarks	Reference No
Children with Wilms tumor Metastatic tumor							71—u
Surgery + post-operative irradiation + vincristine + actinomycin D	Both lungs	Megavoltage or the equivalent	1 400 rad				
	Liver*		3 000 rad	25—28		*Remaining kidney must be protected **Doses comparable to those delivered to the liver	
	Brain, bones, lymph nodes**						
Pre-operative vincristine + surgery + post-operative irradiation + vincristine + actinomycin D							
Testis							
Seminoma Series I (T0 to T4 N0 M0)							71—v
Castration + irradiation	Inguinal, iliac and para-aortic node areas	Supervoltage	3 000 rad	21—28	1 000 rad/week		
Castration + irradiation + cyclophosphamide							
Series II (T0 to T4 N1 to N2 M0)							
Castration + irradiation	Inguinal, iliac and para-aortic node areas	Supervoltage	3 000—4 500 rad	35—42			
	Mediastinum		3 000 rad	21—28			
	Left supraclavicular area		3 000 rad				

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractiona tion	Remarks	Ref er ence No
Castration + irra diation + cyclophos-phamide							
Series III (T0 to T4 N1 to N2 M1)							
Castration + irra diation + cyclo-phospham de	Inguinal iliac and para aortic node areas	Super voltage	4 500 rad	35—42	1 000 rad/week		
	Mediastinum		3 000 rad	21—28		If one single pulmonary metastasis 3 000 rad	
	Left supra clavicular area		3 000 rad			*2 subgroups	
	Involv d organs		3 000—4 000 rad			A = no metastases in parenchymal organs	
Castration + irra diation + cyclo-phosphamide + m thylhydrazine						B = metas tases in parenchymal organs no radiation therapy	
Germinati e tumors other than pur eminoma							71—w
Serie I (T0 to T4 N0 M0)							
Castrat on + rra d at on	Ingu nal iliac and para aortic node areas	S per voltage	4 500 rad	35—42	800—1 000 rad/week		
Ca t at on + irra d ation + act no-myc n D							
S ries II (T0 to T4 N1 to N2 M0)							
Castrat on + rra diation + actino-	Inguinal I ac nd	S p r oltage	5 000 rad	35—42			

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
mycin D	para aortic node areas						
	Mediastinum left supra clavicular area		4 000— 4 500 rad	28— 35			
Castration + irradiation + actino mycin D + cyclo phosphamide + methotrexate							
Series III (T0 to T4 N1 to N2 M1)							
Same treatment groups as in Series II	Metastases depending on tolerance	Super voltage	4 000— 4 500 rad*	35		*For each localisation	
Breast							
Stages I and II							69—94
Radical mastectomy + irradiation	*Publications* NISSEN MEYER R Preliminary report from the Scandinavian Adjuvant Study Group Abstracts Tenth International Cancer Congress p 499 1970						
Radical mastectomy + irradiation + cyclophosphamide	KJELLGREN K Preliminary report from the Scandinavian Adjuvant Study Group surgical aspects Abstracts Tenth International Cancer Congress p 499 1970						
Stages I and II							69—95
Surgery + irradiation (stage I post operative stage II Pre and post operative) Surgery + pre and post operative cyclophosphamide	The hemi thoracic surface the axillary supraclavi cular and parasternal lymph nodes	220 kV HVL 1 6 mm Cu FSD 40 cm	5 500— 6 000 rad	55— 60	150 rad/day	Special technique for the hemithoracic surface with 4 tangential fields	
Stages I and II							69—96*
Mastectomy							
Mastectomy + post operative irradiation	Restrosternal space (between	Gamma irradiation	4 000— 5 000 R	28— 35	200—300 R/day	Preliminary report published in 1968 All	

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Mastectomy + thiotepa Mastectomy + cyclophosphamide	1st & 7th costal cartilages) *infra* and supraclavicular spaces					Union Cancer Congress *Publication* in preparation at present	
Age 35—70 Radical surgery Pre operative irradiation + radical surgery Radical surgery + cyclophosphamide	Breast Thoracic wall	*Co*	*5 500* R/T	*30*	*250 R/T* daily		69— 97
T1– T2 N0—N1 M0 Age Over 50 Removal of the lump under cytotoxic cover + *irradiation*	1st step Breast *Internal* mammary chain	Linear accelerator	3 800 rad	21			69— 99
	2nd step Axillary and supraclavicular areas	Conventional radiation	3 000 rad	15			
	Internal mammary supraclavicular axillary fields		3 000 rad (skin dose)	21	1 000 rad/ week		
Radical mastectomy *performed* under cytotoxic cover + irradiation						*1st & 2nd* steps	
T1 to T3 N0 to N2 M0		Linear accelerator					70— 42

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Radical mastectomy + post operative irradiation	Scar region Parasternal area (8 cm × 10 cm)	Electrons (8 MeV)	4 000 rad	90	3 × weekly (20 fractions)		
	Supra and infraclavicular, axillary node areas (8 × 15 cm)	Roentgen (10 MeV)			3 × weekly (20—22 fractions)		
Radical mastectomy + post operative irradiation + 5 fluorouracil							
Radical mastectomy + post operative irradiation + 5 fluorouracil + cyclophosphamide + mitomycin C							
Bone							
Children with Ewing sarcoma						Study closed and *completed*	69—154
Surgery: No further treatment							
Surgery: Vincristine + Cyclophosphamide							
Irradiation: No further treatment		Super voltage	7 000 rad	48			
Irradiation: Vincristine + cyclophosphamide							

Compared groups	Target volume	Type of radiation	Tumor dose	Overall time (days)	Fractionation	Remarks	Reference No
Children with rhabdomyosarcoma							69—156
Surgery + irradiation (controls)	Tumor	Super voltage	6 000 rad	40	1 000 rad/week (30 fractions)		
	Nodes		6 000 rad				
Surgery + irradiation + chemotherapy							
Neurology							
Children with neuroblastoma							69—158
Surgery + postoperative irradiation		Supervoltage	1 800—4 000 rad*	14—28	5—6 × weekly (1 000—1 200 rad/wk)	*Depending on age	
Surgery + postoperative irradiation + cyclophosphamide							
Malignant glioma Surgery + Continued conventional therapy (controls)						No additional chemotherapy or irradiation but continued general care in the same fashion as those patients receiving drug or irradiation	71—x
BCNU (80 mg/d × 3 q 6—8 wks)							
Irradiation	Whole brain	Co	6 000 rad	42—56			
BCNU + irradiation							

7 Radiation therapy plus surgery plus chemotherapy plus immunotherapy

Compared groups	Target volume	Type of radiation	Tumor dose	Over all time (days)	Fractionation	Remarks	Reference No
Lung							
Surgery + irradiation + long term combined chemotherapy* + No further treatment Specific and nonspecific immunotherapy	Tumor mediastinum and supraclavicular node areas	^{60}Co or betatron	5 000—6 000 rad	42		*Randomization after chemotherapy	10—11